UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: February 25, 2010

SUBJECT: Transmittal of the Meeting Minutes of the FIFRA SAP Meeting Held December 1-3, 2009 on the Scientific Issues Associated with "Field Volatilization of Conventional Pesticides"

TO: Steven Bradbury, Ph.D.
Acting Director
Office of Pesticide Programs

FROM: Sharlene Matten, Ph.D.
Designated Federal Official
FIFRA SAP Staff
Office of Science Coordination and Policy

THRU: Laura Bailey
Executive Secretary, FIFRA SAP
Office of Science Coordination and Policy

Frank Sanders
Director
Office of Science Coordination and Policy

Please find attached to this memorandum the meeting minutes of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) open meeting held in Arlington, Virginia on December 1-3, 2009. This report addresses a set of scientific issues associated with "Field Volatilization of Conventional Pesticides."

Attachment

cc:
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SAP Minutes No. 2010-02

A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

Field Volatilization of Conventional Pesticides

December 1-3, 2009
FIFRA Scientific Advisory Panel Meeting
held at
One Potomac Yard
Arlington, Virginia

NOTICE

These meeting minutes have been written as part of the activities of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP). The meeting minutes represent the views and recommendations of the FIFRA SAP, not the United States Environmental Protection Agency (Agency). The content of the meeting minutes does not represent information approved or disseminated by the Agency. The meeting minutes have not been reviewed for approval by the Agency and, hence, the contents of these meeting minutes do not necessarily represent the views and policies of the Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute a recommendation for use.

The FIFRA SAP is a Federal advisory committee operating in accordance with the Federal Advisory Committee Act and established under the provisions of FIFRA as amended by the Food Quality Protection Act (FQPA) of 1996. The FIFRA SAP provides advice, information, and recommendations to the Agency Administrator on pesticides and pesticide-related issues regarding the impact of regulatory actions on health and the environment. The Panel serves as the primary scientific peer review mechanism of the Environmental Protection Agency (EPA), Office of Pesticide Programs (OPP), and is structured to provide balanced expert assessment of pesticide and pesticide-related matters facing the Agency. FQPA Science Review Board members serve the FIFRA SAP on an ad hoc basis to assist in reviews conducted by the FIFRA SAP. Further information about FIFRA SAP reports and activities can be obtained from its website at http://www.epa.gov/scipoly/sap/ or the OPP Docket at (703) 305-5805. Interested persons are invited to contact Sharlene R. Matten, Ph.D., SAP Designated Federal Official, via e-mail at matten.sharlene@epa.gov.

In preparing these meeting minutes, the Panel carefully considered all information provided and presented by EPA, as well as information presented in public comment. This document addresses the information provided and presented by EPA within the structure of the charge.

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A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

Field Volatilization of Conventional Pesticides

December 1-3, 2009
FIFRA Scientific Advisory Panel Meeting
held at
One Potomac Yard
Arlington, Virginia

Kenneth M. Portier, Ph.D.
FIFRA SAP Session Chair
FIFRA Scientific Advisory Panel

Date: 2/25/10

Sharlene R. Matten, Ph.D.
Designated Federal Official
FIFRA Scientific Advisory Panel
Staff

Date:
2/25/10

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December 1-3, 2009

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INTRODUCTION

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed its review of the Agency's analysis of **Scientific Issues Associated with Field Volatilization of Conventional Pesticides**. Advance notice of the SAP meeting was published in the *Federal Register* on **September 16, 2009**. The review was conducted in an open Panel meeting December 1-3, 2009 held at One Potomac Yard, Arlington, Virginia. Materials for this meeting are available in the Office of Pesticide Programs (OPP) public docket or via Regulations.gov, Docket No. EPA-HQ-OPP-2009-0687. Dr. Kenneth Portier chaired the meeting. Dr. Sharlene Matten served as the Designated Federal Official. Dr. Stephen Bradbury, Deputy Office Director for Programs, OPP, and Dr. Tina Levine, Director, Health Effects Division, OPP provided opening remarks at the meeting. Presentations of technical background materials were provided by Mr. Jeff Evans, Mr. Charles Smith, Dr. Judy Facey, and Dr. Elizabeth Mendez from the Health Effects Division, OPP; Dr. Faruque Khan, Mr. Chuck Peck, and Mr. Gabe Rothman from the Environmental Fate and Effects Division, OPP; and Ms. Annie Jarabek, National Center for Environmental Assessment, Office of Research and Development.

The *Standard Operating Procedures for Residential Exposure Assessment, i.e.*, Residential SOPs, is a set of standard instructions for estimating residential exposure resulting from various direct, labeled pesticide uses. Individuals in residential settings can also be potentially exposed via indirect exposure to conventional pesticides. These types of exposures can occur through a variety of means including field volatilization of conventional pesticides, spray drift, and take-home exposure. Methodologies for assessing indirect exposures are not currently included in the Residential SOPs.

Recently, the Agency has been exploring the development of an approach for assessing inhalation exposure resulting from the field volatilization of conventional pesticides. The following issues have been identified as key elements for this exposure scenario:

1) Use of the Agency's Reference Concentration (RfC) methodology to calculate Human Equivalent Concentrations (HECs) when inhalation toxicity studies are available.

2) Comparison of the use of inhalation vs. oral toxicity studies.

3) Development of a tiered approach to determine the level of complexity and refinement needed to estimate exposure, including:

    a) Use of available air monitoring data: California Air Resource Board (CARB), Pesticide Action Network – North America (PANNA), and other data sources.
    b) Development of a volatilization screening tool to estimate flux based on physicochemical properties of a pesticide.
    c) Use of more refined soil models to estimate flux.
    d) Use of air models to estimate concentrations around a treated field.

EPA's goal is to have a set of procedures that include transparent methodologies and data inputs that will guide the assessment of bystander exposure resulting from field volatilization of conventional pesticides in a straight-forward and user-friendly fashion. The Agency sought

comment from the Panel on the adequacy of the toxicological and exposure assessment methodologies; the applicability, analysis, and use of available air monitoring data; the strengths and limitations of the models being considered by the Agency for predicting flux of conventional pesticides; and the overall presentation of the issues related to field volatilization of conventional pesticides with respect to scientific integrity and public transparency.

PUBLIC COMMENTERS

Oral statements were presented by:

1. Susan Kegley, Ph.D., Principal and CEO, Pesticide Research Institute on behalf of Pesticide Action Network

2. Larry Jacobs on behalf of Jacobs Farm/Del Cabo Inc.

3. Jennifer Sass, Ph.D. on behalf of the Natural Resources Defense Council and others

Written statements were provided by:

1. Kenneth Racke, Ph.D. on behalf of Dow AgroSciences, LLC

2. Carol Dansereau on behalf of Farm Worker Pesticide Project

3. Jennifer Sass, Ph.D., National Resources Defense Council (NRDC) on behalf of Natural Resources Defense Council and others

4. Susan Kegley, Ph.D. Principal and CEO, Pesticide Research Institute on behalf of Pesticide Action Network - North America

5. Larry Jacobs on behalf of Jacobs Farm/Del Cabo, Inc.

6. Anne Katten on behalf of California Rural Legal Assistance Foundation

7. Dona Hippert and Lisa Arkin on behalf of Oregon Toxics Alliance

8. Jorga Stewart, private citizen

9. Carolyn Ashlock and Warren Trotter, private citizens

10. Lynn Bower, private citizen

11. Jan Wroncy, Gaia Visions, private citizen

12. Tom Kerns, private citizen

13. Maxine Centala, private citizen

14. Jean Public, private citizen

SUMMARY OF PANEL DISCUSSION AND RECOMMENDATIONS

TOPIC A: Exposure Assessment Issue

Traditionally, the Agency's assessment of bystander inhalation exposure to volatile pesticides has relied extensively on the use of air monitoring data. However, for the fumigants, an exposure assessment methodology was developed that combined the use of air models and air monitoring data. The Agency has taken the exposure assessment methodologies developed for the fumigants and further adapted them by utilizing soil models to predict field volatilization of conventional pesticides from plant and soil surfaces. Based on this premise, the Agency has identified several key factors for consideration by the Panel. They include the evaluation of the approaches and data sources used in the tiered exposure estimation methodology and use of soil models for predicting flux of conventional pesticides. Specifically, the Agency identified the following issues for the Panel to consider:

1. Tier I Approach for Identifying Volatile Chemicals of Concern for Risk Assessment, Air Concentration. The Tier I approach incorporates the use of vapor pressure alone to arrive at a saturated concentration in air. The estimated air concentration can be compared with available toxicity data to evaluate inhalation exposure concerns to human and other terrestrial organisms.

   Please comment on the Agency's approach for using the Tier I air concentration estimation method as a screening procedure. Please discuss the strengths and limitations of the screening approach. Please identify any alternative methods and/or physical-chemical properties, if any, which may be utilized as a screening procedure to identify chemicals with potential inhalation exposure concerns.

Panel Response

The Panel chose to combine its response to Question 1 with that of Question 2a (see below).

2. Tier II Approach for Identifying Volatile Chemicals of Concern for Risk Assessment, Volatility and Flux Models. Two options are being considered to refine the Tier I estimation method. Option A incorporates the use of physical-chemical properties including application rate, vapor pressure, solubility, and K_{oc} in an empirically-derived function to estimate flux rates. This option has less [sic] constraints and requires fewer input parameters to generate flux rates as compared to Option B described below.

   a. *Given the state of the science, please comment on the applicability of using the Option A model to predict flux rates. Please discuss the strengths and limitations of this approach and how these impact the results. Please identify any alternative methods, if any, which may be utilized to identify chemicals with potential inhalation exposure concerns.*

Panel Response to Questions 1 and 2a

The Panel identified problems regarding the use of a single vapor pressure value to arrive at a saturated vapor concentration for a Tier I approach for identifying volatile chemicals of concern. The major finding was that this approach has only a limited connection with how a pesticide is actually used in the real world, *e.g.,* as a formulation perhaps diluted in water with other additives like surfactants that may increase or decrease the effective vapor pressure relative to the active ingredient(s) value in its pure form. Therefore, the proposed Tier I approach may generate concentration predictions that are higher or lower than actually found in field measurements and will not necessarily provide predictions that are protective.

The Panel suggested that an alternative to the use of the proposed Tier I approach is to use the Woodrow et al. (1997) correlation approach to estimate a maximum 24-hour flux value. This approach is based on correlations between measured data and the physicochemical properties of the compounds, and it does not require an inordinate amount of data. This regression could be updated with all the latest studies and other relevant factors to increase its accuracy, a sensitivity analysis could be conducted on the model, then additional safety factors could be used to make it more protective as needed for a Tier I approach.

Tier II, Option B, is a refined process that utilizes fate and transport models to predict flux rates of applied pesticides that off-gas from treated fields. Current fate and transport models consider mechanisms related to volatilization, biodegradation, abiotic degradation, physicochemical properties, runoff, crop uptake, and leaching to account for the transformation and movement of the entire initially applied material. Volatilization mechanisms from bare soil and crop canopy surfaces are also important processes that the Agency believes ought to be considered to fully account for volatilization and diffusion from the vadose zone and canopy into the atmosphere. The Agency has utilized two models, the Pesticide Root Zone Model (PRZM) and the Pesticide Emission Assessment at Regional and Local Scales (PEARL) that incorporate these mechanisms and have the utility for the prediction of flux rates from treated fields. Option B requires extensive knowledge on environmental fate properties, as well as information related to application site, crop management and meteorology.

b. Please comment on the applicability of using fate and transport models to predict flux rates given the state of the science. Please discuss the strengths and limitations of both models and how these impact the results. Please identify any fate and transport model(s) which the Agency has not considered in this analysis which would be applicable for pesticide applications and crop management scenarios.

Panel Response

The Panel agreed that the concept of coupling a fate and transport model, such as PRZM or PEARL, to predict fluxes, with a model, such as the Pesticide Exposure Risk Model for Fumigants Model (PERFUM), to estimate air concentrations at different distances from the field is a sound Tier II approach for identifying volatile chemicals of concern within the confines of evaluating pesticide volatilization in treated fields (excluding spray drift). The Panel noted that

while dispersion models, such as PERFUM, have been validated for fumigants, they have not been validated for semi-volatile pesticides. In addition, models such as PRZM or PEARL have also not been sufficiently validated for predicting semi-volatile pesticide volatilization from soil or crops. The Panel stated that rather than basing volatile flux prediction models on back-calculation methods, such models should be validated with direct field measurements of flux under different cropping patterns, application techniques, rates, and frequency, and in different geographic regions. The Panel proposed that the Pesticide Emissions Model (PEM) (Scholtz *et al.,* 2002a, b) be considered as a promising peer-reviewed, alternative model to predict flux rates of semi-volatile pesticides in treated fields.

TOPIC B: Toxicological Assessment Issues

As the Agency's understanding of the state-of the science in inhalation toxicology has evolved so has the Agency's approach to conducting inhalation hazard and risk assessments. This evolution has seen the Agency move from converting oral doses to inhalation concentrations to using the RfC methodology and/or physiologically-based pharmacokinetic (PBPK) models. As OPP continues to work on refining the risk assessment paradigm, the Agency is seeking the SAP's input on a number of key factors. They include the use of oral toxicity studies when inhalation studies are not available and the use of aerosol inhalation toxicity studies to represent toxicity to vapors of the same chemical. Specifically, the Agency identified the following issues for the Panel to consider:

B.1) The analysis conducted by the Agency indicates that, in general, oral toxicity studies may not accurately represent the full spectrum of toxic effects that may occur as a result of inhalation exposure. The analysis also indicates that - unless the same endpoints are identified through both routes of exposure - oral toxicity studies frequently underestimate toxicity by the inhalation route. The Agency has not been able to discern any patterns in this under/over estimation. *Please comment on any potential patterns that the Agency has not identified.*

Panel Response

The Panel concluded that route-to-route extrapolations using oral toxicity data to assess toxicity via the inhalation route is only scientifically justified, if a validated PBPK model is available or if the pesticide falls into Category 3 chemicals according to the Agency's Inhalation Reference Concentration (RfC) classification scheme (*i.e.*, those gases/vapors that cause systemic effects and not point-of-entry effects) (EPA, 1994) and the following criteria are also met.

a. The toxicological effect of concern is systemic for both entry routes and this effect is independent of route of exposure.

b. The first pass effects in the liver for oral exposure and in the respiratory tract for inhalation exposure are minimal to nonexistent or, if there is some first pass effect, the metabolism following exposure is the same for both exposure routes.

c. The chemical will not be chemically modified by the gastrointestinal bacteria or enzymes or by the acidic environment in the stomach differentially than it would be in the more

neutral to slightly basic environment of respiratory tract fluids. Pesticide stability in gastric fluid should be of primary concern in considering the use of oral exposure data. If the compound is not stable in gastric fluid, the toxicological data on oral dosing would be of little to no value in estimating any inhalation toxicity.

d. The absorption efficiency for oral and inhalation exposure must either be identical or known, so that accurate values may be incorporated into any model. The absorption efficiency for oral and inhalation exposure must either be identical or known, so that accurate dose values may be incorporated into any model; the use of a default value of 1 for absorption is not justifiable in the absence of any data. Furthermore, the absorption cannot be differentially influenced by a toxic response unless this response is the same via both routes and/or is influenced by relatively the same extent via both routes.

Even when the above criteria may be met, the Panel recommended an additional Uncertainty Factor (UF) of 10 for the final extrapolation for inhalation toxicity from oral toxicity data. The Panel stated that the use of uncertainty factors is not a replacement for more accurate models and data from more inhalation toxicity studies. The Panel strongly recommended that the Agency obtain additional inhalation toxicity data if such data are not available and if the vapor form of the pesticide does not meet the criteria for route-to-route extrapolation as described above.

The Panel suggested that some of the problems associated with route-to-route extrapolation from oral toxicity studies to inhalation toxicity studies might be evaluated by simple *in vitro* studies, such as solubility and stability in simulated gut or lung fluid, or by consideration of the chemical structure of the pesticide and using structural activity relationships.

The Panel made the following additional comments with regard to route-to-route extrapolation:

a. The Panel discussed several problems with the way in which EPA used Haber's Law (or Rule), in making adjustments for the duration of exposure when calculating HECs from repeated exposure inhalation toxicity studies.

b. The Panel noted two problems with the IEC equation. First, species differences in surface area/body weight are not accounted for, so that the equation needs to be modified. In cases for pesticides in Category 3 where route-to-route extrapolation may be justified, it would be better to adjust the animal oral dose to a human equivalent oral before further adjusting this value to an IEC for humans.

c. The Panel recommended that the Agency consider Benchmark Dose (BMD) analysis when concentration-response data are available and are amenable to modeling.

B.2) For a significant number of conventional pesticides, inhalation toxicity studies are not available. *Please comment on the scientific strengths and weaknesses of available approaches that may be used in the interim to assess inhalation hazard in the absence of inhalation toxicity studies.*

Panel Response

Overall, the Panel strongly recommended that the Agency conduct additional inhalation toxicity studies to adequately assess inhalation hazard. One Panel member provided a summary of alternative approaches reported in the literature that have been used to assess inhalation hazard in the absence of inhalation toxicity studies, *e.g.*, "threshold of regulation" or "threshold of no toxicological concern" (see Appendix C for a discussion of these procedures). The Panel stated that these approaches should not be used in the interim to assess inhalation hazard for pesticides in the absence of inhalation toxicity studies for the following reasons. These screening approaches do not involve a chemical-specific hazard identification or dose-response assessment and were originally developed to assess oral hazard in the absence of oral toxicity studies, and not inhalation hazard. While in a few cases the methodology has been used to evaluate inhalation hazard, the exposure durations in these cases (*i.e.*, chronic, lifetime exposure and one-hour intermittent exposure) do not correspond to the exposure durations the Agency is evaluating.

B.3) For inhalation toxicity studies the test material is typically aerosolized. After volatilization, however, the Agency anticipates exposures to vapors rather than the aerosolized particles. *Please comment on the predictive capabilities of aerosol studies to identify potential toxic effects and/or quantify the dose-response resulting from exposure to vapors. Is the Panel aware of any studies that quantitatively compare inhalation toxicity after exposure to vapors and aerosols? In the absence of such data, can the Panel recommend an approach to account for the potential differences between vapors and aerosols?*

Panel Response

The presence of a semi-volatile organic compound in either the vapor or particle phase will have impacts on site of deposition, absorption, and potentially dose and toxicity. The biological impact of the relative portions in each phase, however, has been poorly studied. Therefore despite known mechanisms for potential differences in dose and absorption, the ability to predict toxicity of vapors from aerosol studies is fairly limited. The Panel knew of no studies that have investigated the health impact of exposure to a single semi-volatile chemical under different phases. Some studies with mixtures have utilized techniques to either remove the particulate phase by filtration or the vapor phase by using a denuder to study the role of those materials independently (McDonald *et al.*, 2007). In many cases, the removal of the particulate phase of the mixture has not resulted in biological effects that differ from those obtained with the total mixture, especially for systemic effects. These mixture studies, however, may not be appropriate to answer questions related to a single component study. The Panel stated that there remain fundamental questions (beyond just the deposition site) related to the relative toxicity of vapors and particles. These must be considered as adding uncertainty when attempting to predict biological effects from exposure to the vapor versus particulate form of any given pesticide.

The Panel noted that any aerosol study of a semi-volatile compound will include that compound in both the vapor and particle phase. As a result, previous inhalation toxicity studies for semi-volatile pesticide registration contained the vapor phase of that compound in the aerosol.

Unfortunately, the studies conducted for pesticide registration did not measure the vapor portion of the mixture. The exposure monitoring in the inhalation toxicology studies was conducted with measurement of either weight gain or chemical content on filters that were used to trap the aerosol. That approach only measured the particle portion of the aerosol and the vapor that may have adsorbed on to the filter during sample collection. The vapor portion, which would have been present in these atmospheres, was not measured.

ADDITIONAL DISCUSSIONS ON INHALATION TOXICITY

The Panel discussed various topics as an outgrowth of the charge questions.

1. *Appropriate averaging times and sampling devices for field measurements of volatilized pesticide.* The Panel recommended that the Agency collect exposure data with shorter collection times than 24-hours and to use these data in health effects evaluations.

2. *Protocols for new inhalation toxicity studies (possible experimental designs).* The Panel recommended that inhalation toxicity studies should be conducted with durations of exposure of up to 90 days.

3. *Uncertainty factors for quality of the database and what constitutes a minimum database.* The Panel recommended that EPA establish criteria for short-term studies (*e.g.,* 1, 7, 14, 28 days) and that they use an additional UF of 10, if only a minimum database is available for their assessment.

4. *Moving toward a cumulative or total risk assessment.* The Panel recommended that total exposure be assessed to more fully encompass all types of inhalation exposures for the risk assessment process. The hazard quotient (HQ) or similar approach should be considered to assess risk from each of the types of exposure that contribute to the total potential exposure following application of pesticides.

TOPIC C: Risk Assessment Issues

The Agency discussed its methodology for combining the exposure estimation methodologies and inhalation toxicological approaches to estimate postapplication bystander inhalation risks resulting from field volatilization of conventional pesticides. In estimating postapplication bystander inhalation risks, there are a few principles that should be followed: (1) It is important to properly match the duration of the exposure with a proper toxicity study of comparable duration. (2) Both dissipation of air concentrations around a treated field as well as when retreatment of the field may occur need to be considered. (3) Clearly define the uncertainties and limitations of this type of assessment. The Agency has identified the following issues for the Panel to consider with respect to estimating postapplication bystander inhalation risks:

Please comment on the strengths and limitations of the Agency's use of the empirical and modeled air concentrations in the provided risk assessment case study. Does the Panel agree that the postapplication bystander inhalation risk estimate case study appropriately matches

the duration of the exposure with the proper toxicological study of the same duration? Please comment on the scientific strengths and weaknesses of conclusions and characterization regarding the estimated risks presented in the case study.

Panel Response

C.1) Please comment on the strengths and limitations of the Agency's use of the empirical and modeled air concentrations in the provided risk assessment case study.

The strengths and weaknesses of the use of the Woodrow empirical model to assess risk are much the same as the Panel discussed related to Topic A, Question 2a (see above). The main strength of this model is its basis in multiple studies over a wide range of vapor pressures; a secondary strength is that its results are in the range of the results of the air concentrations estimated by more sophisticated computer-modeled air concentrations. The limitations of the empirical model are that it is based on a limited range of crops, weather, and locations, and does not take into account the potential effect of an activity coefficient on vapor pressure, and it is applicable only to the first day post-application.

The strengths of the computer-based modeled air concentrations are that they can account for dynamic changes in post-application conditions and residue history. Their weaknesses are the limited knowledge that users have of the internal components of these models, the concern that the components do not model evaporation from foliage as well as they model evaporation from soil, and that the particular analyses presented to the Panel inappropriately decoupled the variance of the flux from the variance of dispersion.

C.2) Does the Panel agree that the postapplication bystander inhalation risk estimate case study appropriately matches the duration of the exposure with the proper toxicological study of the same duration?

The Panel agreed that the case study appropriately matched the duration of the exposure with the proper toxicological end point, although there were some questions regarding the specificity of the target population within this particular case study. Again, a great deal of the Panel's discussion on Topic B apply here, particularly the limitations of the route-to-route extrapolation process and the need to apply toxicological data collected from one exposure to another. Thus, the success of this case study to achieve its goal is tempered by the limited confidence that the Panel has in extrapolating toxicological data considering both route and duration of the exposure.

However, in a broader sense, the Panel agreed that the example did not adequately consider the ability to model differences in duration of the exposure. In earlier sections, the Agency presented three types of exposure scenarios for risk assessment, short- (up to 30 days), intermediate- (up to 90 days) and long-term (greater than 1 year). The example only presented modeled air concentrations for short-term exposures. The models did not estimate intermediate and long-term exposures. Two of the five pesticides listed in Table 3 (of the Agency's background document) used for modeling short-term exposures have reported soil

half-lives of greater than 150 days, illustrating that intermediate exposures from single applications may occur. The Panel recommended the Agency consider adding longer term exposures of more than 30 days in the models to address intermediate and long-term chronic exposures and to match toxicological studies.

C.3) Please comment on the scientific strengths and weaknesses of conclusions and characterization regarding the estimated risks presented in the case study.

The Panel broadly agreed that the case study included all or most of the important elements to conduct a proper risk assessment. The strength of the inhalation toxicity and exposure data bases for the chemical chosen led the Panel to conclude that the inhalation hazard and exposures assessments, and Margin of Exposure (MOE) analysis were realistic based on field monitoring data. However, the Panel had a range of recommendations for how this model and the risk assessment process could be improved, and reservations if such an analysis were applied to many other chemicals. For instance, the toxic endpoints are unlikely to be as strong for other chemicals, the details and general applicability of some steps in the process were not well-defined, PRZM or PEARL were not optimized for their application to the evaporation of semi-volatile pesticides, and the impact of the propagation of uncertainty and safety factors within the process on the final result is uncertain. An alternative risk assessment approach based on the Volatilization Hazard Ratio (VHR) was presented and the case study chemical was evaluated using this approach.

DETAILED RESPONSES TO CHARGE QUESTIONS

TOPIC A: Exposure Assessment Issue

Traditionally, the Agency's assessment of bystander inhalation exposure to volatile pesticides has relied extensively on the use of air monitoring data. However, for the fumigants, an exposure assessment methodology was developed that combined the use of air models and air monitoring data. The Agency has taken the exposure assessment methodologies developed for the fumigants and further adapted them by utilizing soil models to predict field volatilization of conventional pesticides from plant and soil surfaces. Based on this premise, the Agency has identified several key factors for consideration by the Panel. They include the evaluation of the approaches and data sources used in the tiered exposure estimation methodology and use of soil models for predicting flux of conventional pesticides. Specifically, the Agency identified the following issues for the Panel to consider:

A.1) Tier I Approach for Identifying Volatile Chemicals of Concern for Risk Assessment, Air Concentration. The Tier I approach incorporates the use of vapor pressure alone to arrive at a saturated concentration in air. The estimated air concentration can be compared with available toxicity data to evaluate inhalation exposure concerns to human and other terrestrial organisms.

Please comment on the Agency's approach for using the Tier I air concentration estimation method as a screening procedure. Please discuss the strengths and limitations of the screening approach. Please identify any alternative methods and/or physical-chemical properties, if any, which may be utilized as a screening procedure to identify chemicals with potential inhalation exposure concerns.

A.2) Tier II Approach for Identifying Volatile Chemicals of Concern for Risk Assessment, Volatility and Flux Models. Two options are being considered to refine the Tier I estimation method. Option A incorporates the use of physical-chemical properties including application rate, vapor pressure, solubility, and K_{oc} in an empirically-derived function to estimate flux rates. This option has less [sic] constraints and requires fewer input parameters to generate flux rates as compared to Option B described below.

a. Given the state of the science, please comment on the applicability of using the Option A model to predict flux rates. Please discuss the strengths and limitations of this approach and how these impact the results. Please identify any alternative methods, if any, which may be utilized to identify chemicals with potential inhalation exposure concerns.

Tier II, Option B is a refined process which utilizes fate and transport models to predict flux rates of applied pesticides which off-gas from treated fields. Optimum fate and transport models consider mechanisms related to volatilization, biodegradation, abiotic degradation, physicochemical properties, runoff, crop uptake, and leaching to account for the transformation and movement of the entire initially applied material. Volatilization

mechanisms from bare soil and crop canopy surfaces are also important processes, which the Agency believes ought to be considered to fully account for volatilization and diffusion from the vadose zone and canopy into the atmosphere. The Agency has utilized two models, the Pesticide Root Zone Model (PRZM) and the Pesticide Emission Assessment at Regional and Local Scales (PEARL) which incorporate these mechanisms and have the utility for the prediction of flux rates from treated fields. Option B requires extensive knowledge on environmental fate properties, as well as information related to application site, crop management and meteorology.

b. Please comment on the applicability of using fate and transport models to predict flux rates given the state of the science. Please discuss the strengths and limitations of both models and how these impact the results. Please identify any fate and transport model(s) which the Agency has not considered in this analysis which would be applicable for pesticide applications and crop management scenarios.

Panel Response to Questions 1 and 2a

During the progression of the panel discussion, Questions 1 and 2a became linked. Therefore, the Panel combined its response to Question 1 with that of Question 2a.

Vapor pressure clearly is an important physical property in evaluating the behavior of pesticides, especially with respect to volatilization from plant surfaces. However, the Panel concluded that the use of the Tier I approach for identifying volatile chemicals of concern was overly simplistic and of no real value as a screening tool. The Panel identified four major issues with the Tier I screening approach (discussed below). The Panel proposed the Woodrow *et al.* (1997) correlation approach as an alternative to the proposed Tier I approach (referred to as Tier II Option A within the EPA background document, p. 24) to estimate a maximum 24-hour flux value that then could be used to calculate a maximum air concentration over 24-hours.

Major Issues with the Tier I Approach

This report has organized the Panel's responses into the following four groups of topics: overestimation of air concentrations, temperature considerations, low vapor pressure (VP) pesticides, and pesticide formulation considerations.

1. *Overestimation of air concentrations.* The saturated vapor concentration calculated from vapor pressure appears to generally over-predict the maximum concentration measured in field settings by such a wide margin as to make the predictions useless. In the examples within the EPA background document paper, *i.e.,* Table 4, p. 36, the proposed Tier I approach overestimates the observed concentrations by about two orders of magnitude when the pesticide is on foliage and five orders of magnitude when on soil.

   Vapor pressure is the sole variable both in the Tier I model and in the Tier IIA model for volatilization following foliar applications.[1] Vapor pressure also plays a central role in

[1] In contrast, both of the Tier IIB methods (PRZM and PEARL) use Henry's law constant instead of vapor pressure (that constant is related to VP, as will be discussed *circa* Eqn. A4 below). .

the Tier IIA model for volatilization from soil as evidenced from the 0.88 R^2 correlation between log flux and just the log VP across the 10^6 range of VP values used to derive that model (Woodrow *et al.*, 1997). However, as a simple predictor, the Tier I model over-estimated the maximum measured field concentrations of the pesticides presented in Table 4 of the Agency background document (p. 36). The over-estimates for the four chemicals applied to foliage ranged from factors of 12- to 174-fold (with a geometric mean of 48-fold); however, the over-estimate for the one soil application (Chemical D) was 27,472 times greater than its maximum monitored concentrations. Thus, at first glance. Thus, at first glance, the Panel concluded that a simple comparison of vapor pressure to toxicity was too conservative to be useful.

In contrast to the above generalization, several recent studies conducted in the United Kingdom showed errors in the opposite direction. One Panelist reported on studies (sponsored by the UK Department for Environment Food and Rural Affairs, Defra) in which the air concentrations of two of the five pesticides studied were higher following application than the concentration predicted by the Tier I model. In particular, the air concentrations of epoxiconazole and prothioconazole were higher than predicted by the Tier I model. A summary of these findings is presented below while a more detailed report on these data is provided in Appendix A. In the first of these studies (Bulter-Ellis and Miller, 2008; Figure A-2 of Appendix A) in which epoxiconazole was applied to 4.8 hectares of a cereal crop, air concentration at a height of 0.7 meters and 2 meters downwind from the field's edge of a 4.8 hectare 2-3 hours after application was one and a half times the predicted saturated vapor concentration. And in a similar study at another location (Appendix A, Figure A-3), measured air concentrations from 0-90 minutes after application were nearly two times the predicted saturated vapor concentrations. In a second U.K. trial (Defra Project PS2023) conducted in October 2009 at a laboratory independent of the first facility (Table A-4 of Appendix A), the air concentrations of prothioconazole peaked about 8 hours after application at over twice its saturated vapor concentration. These observations cast doubt on the reliability of the proposed Tier I approach in the other direction.

2. *Temperature considerations.* The Tier I model as proposed would use a vapor pressure value based on only a single temperature (typically 20-25°C) and therefore does not provide a realistic prediction of the concentration on hotter than normal days. Temperatures observed in agricultural regions differ significantly from region to region, season to season, or even from day to night, and this variation is enough to change the vapor pressure by a factor of two in either the positive or negative direction.

   Vapor pressure should be described as a function of temperature. Surface temperature should be used in the models to estimate volatilization from the earth's surface. One panelist commented that possibly some of the pesticide behavior observed in the UK data presented in Appendix A could be due to the difference between surface temperature and air temperature. A pesticide will volatilize in proportion to its vapor pressure at the surface (soil or leaf) temperature that can exceed the air temperature on a sunny day by about 10°C. The temperature of the pesticide residues in the UK studies may not have been accounted for in their reported data. As a rule of thumb, an increase in a liquid's temperature of 12°C (21°F) will increase its vapor pressure by a factor of 2.

3. *Low vapor pressure pesticides.* Vapor pressure data for pesticides with very low vapor pressures can be very difficult to obtain and may be subject to substantial errors and uncertainty. These low vapor pressure substances are the most likely to be 'screened out' by a simple pure vapor pressure approach.

   It is difficult to accurately measure vapor pressures as low as those for the pesticides in the UK studies (*circa* 10^{-7} to 10^{-8} mmHg). For example, for all six of the fourteen pesticides considered by Woodrow *et al.* (2001) that had reported vapor pressure values of less than 10^{-2} mmHg (and these only ranged from 10^{-3} to 10^{-4} mmHg), the reported VP values underestimated the vapor pressure values predicted by their physical characteristics by an average of 1.6-fold.. Thus, the values for the vapor pressure of epoxiconazole and prothioconazole reported in the UK studies may have been in error.

4. *Pesticide formulation considerations.* A pesticide's vapor pressure as a pure chemical [active ingredient(s)] has only a limited connection to its vapor pressure as it is actually used in the real world. For example, pesticides are typically applied as a formulation, perhaps diluted in water with other additives like surfactants, and these factors may elevate the vapor pressure of the active ingredient relative to the pure compound value. Therefore, the proposed Tier I approach may generate concentration predictions that are higher or lower than either the vapor pressure that exists in field conditions or that is actually found in field measurements, and thus will not necessarily provide predictions that are protective. In the case of the UK data, the chemical's vapor pressure in an aqueous mixture on foliage may have been increased beyond that reported for a pure or neat substance. The potential magnitude of that effect is described below. Whether or not an activity coefficient or one of the other explanations described above applies to the recent findings in the UK is unknown at this time; however, unless an explanation can be found, those findings cast doubt on the whole premise of these models.

Predicting a Pesticide's Vapor Pressure in a Mixture

The best model for predicting a chemical's vapor pressure in a mixture is the use of an empirical adjustment to Raoult's law for an ideal mixture (Eqn. A1).[2] Such an adjustment is called an "activity coefficient" and is typically given the symbol γ (a lowercase Greek gamma), and X_i is the molar concentration of the chemical within the mixture. Equation A2 both defines γ_i mathematically and expresses the empirical concept behind it.

$$P_{vapor,\,i} = \gamma_i \times X_i \times P_{vapor} = \gamma_i \times \text{Raoult's predicted } P_{vapor,\,i} \qquad \text{Eqn. A1}$$

$$\gamma_i = \frac{\text{Measured or actual } P_{vapor,\,i}}{\text{Raoult's } P_{vapor,\,i} = X_i \times P_{vapor}} \qquad \text{Eqn. A2}$$

A chemical's activity coefficient is not actually a constant but is broadly a function of both the solvent in which it is mixed and its concentration in that mixture. Figure B-1 in Appendix B

[2] More detailed information on the behavior of vapor pressure in mixtures is provided in Appendix B.

depicts the pattern of γ as a function of X for a few common organic solvents in water. As a component in a mixture gets more and more dilute, its γ value eventually reaches a constant $\gamma\infty$ (the ∞ sign denotes infinite or a very high dilution). The magnitude of some activity coefficients in water is certainly sufficient to cause major deviations from an ideal mixture. For instance, a γ^{∞} of 50 is sufficient to increase a chemical's vapor pressure by a factor of more than 2-fold when it is present in water at molar fraction of 10% to 30%, and a γ^{∞} of 400 or more can increase a chemical's vapor pressure by more than an order of magnitude. Unfortunately in the case of semi-volatile pesticides applied to crops, the pesticide concentration in water is an independent and dynamic variable (a pesticide applied in water may start out dilute, rapidly become concentrated as the water in the droplet evaporates, and potentially become dilute again due to dew, *etc.*). In addition to water, the pesticide is likely to be absorbed into the organic components of a leaf's cuticle, in which a different value of γ would apply.

The Panel acknowledged that the value for a given chemical's $\gamma\infty$ in water can be predicted from its Henry's constant via Eqn. A3 (although to be used quantitatively in that equation, the value of H_i must be in the same units as P_{vapor}).

$$\gamma_i^{\infty} = \frac{H_i}{P_{vapor}} \qquad \text{Eqn. A3}$$

The Panel commented that most of the Tier II, Option B models appear to use a Henry's law constant, although it is not clear just how it is used. Henry's Law allows one to predict the vapor pressure of a component in a water solution based on a fixed empirical coefficient often called a "Henry's Law constant" and denoted by the symbol "H_i" herein. A common expression of Henry's Law might look like Eqn. A4. While such constants are widespread and often available for pesticides, a known limitation of Henry's law is that it only applies to very dilute mixtures. Use of Henry's law for more concentrated mixtures will introduce another set of errors that are only touched on in Appendix B.

$$P_{vapor,i} = H_i \times X_i \qquad \text{Eqn. A4}$$

In principal, an activity coefficient could be applied to Raoult's law to correct any vapor pressure for its non-idea behavior in a mixture. Computer codes have been developed to predict activity coefficients for various mixtures and can be applied to semi-volatile pesticides (Muro-Suñé *et al.*, 2005). However, such an approach may have limited utility as part of a screening tool for these pesticides because the magnitude of the correction depends on the composition of the mixture. The Panel thought that it might be feasible to find the highest product of $\gamma_i \times X_i$, but for a more complete dynamic prediction necessary for a Tier IIB model, every formulation would need to be evaluated separately due to the varying components in applied mixtures. Additionally, any effects due to changing mixture composition and temperature post-application also would need evaluation. This would require a very complex set of computations that go beyond the goals of a Tier 1 approach.

The Woodrow et al. (1997) Approach as an Alternative to the Tier I Approach

The Panel proposed the Woodrow *et al.* (1997) approach as an alternative to the proposed Tier I approach (referred to as Tier II Option A in the EPA background document, p. 24) to estimate a maximum 24-hour flux value that then could be used to calculate a maximum air concentration. The Woodrow approach is based on empirical data in addition to selected physicochemical properties of the compound when applied to soil. It allows for an evaluation of pesticides applied directly to water or plants or incorporated into soil, and yet it does not require an inordinate amount of data. This simplified model could be updated with all the latest studies and other relevant factors to increase its accuracy. A sensitivity analysis could be conducted to refine this model. Additionally, confidence intervals around the model predictions could be calculated and safety factors could be added to the results of the model predictions to make it more protective as needed for a Tier I.

As described in the EPA background document, Woodrow *et al.* (1997) established a correlation (Eqn. A5). between *ln Flux ($\mu g/m^2$ hr)* and *ln [(VP x CF x AR)/(K_{oc} x S_w)]* for soil applied pesticides, where *VP* is vapor pressure (Pa), *CF* is a conversion factor 133.32 Pa/torr, *AR* is the application rate (in units of kg/ha), K_{oc} is the soil organic carbon-water partition coefficient (mL/g), and S_w is the pesticide's aqueous solubility (mg/L.

$$X = 19.35 + 1.0533 \ln\left[\frac{VP \times CF \times AR}{K_{OC} \times S_W}\right] \qquad \text{Eqn. A5}$$

Similar correlations just involving vapor pressure were also developed for pesticides applied to plants or inert surfaces, and pesticides applied to water. While this approach also relies on the vapor pressure of the compound, the correlation is grounded in measured flux data that could be used to calculate a more realistic air concentration value.

The Panel recommended that EPA update the correlation equations published by Woodrow *et al.* (1997) with data published since this work was carried out to strengthen the reliability of predictions, *e.g.*, Leistra *et al.* (2006). In addition, the Panel recommended that additional studies be commissioned by EPA to expand the number of data points in the regression for flux from foliage and flux from soil. Consideration should also be given in future studies to plot designs that can improve the quality of the measured flux data, *e.g.*, see Majewski *et al.* (1990, 1991) for a description of comparing multiple methods for measuring pesticide soil volatilization rates.

Some Panelists were concerned that the Woodrow approach would not adequately assess the potential impact of some spray from foliar applications bypassing the foliage and falling to the soil surface. Several panelists commented that foliage residues would, in most cases, contribute the largest fraction of the total flux to the air, at least for the first 24-hours after application. However, over longer spans of time, flux from the soil could contribute more significantly to the overall flux. However, this issue is a minor concern for the continued use of this model because only the maximum flux rate is used in the correlation and the model only to estimate the maximum flux rate on the first day and not to provide an estimate of subsequent temporal trends

or concentrations beyond the first day. As discussed in Woodrow *et al.* (1997), the Panel suggested that leaf surface area be added as a modifying factor to make the model more robust when applied to different crops. Soil moisture should also be added to refine the soil portion. Pesticides volatilize more rapidly from moist soil than from dry soil, other factors being constant. Other additions aimed toward refining the flux model for soil applications would include the depth of incorporation of the chemical after application, soil temperature, and wind speed at the soil surface.

The Panel noted that there is a lot of uncertainty in the physicochemical data and measuring volatilization fluxes (Majewski, 1996). A major factor in the Woodrow model is the *Koc* term, which is not currently required at pesticide registration. However, a highly correlated measure, *Kow*, *i.e.,* octanol-water partition coefficient (EPA, 1996) is required and if the *Koc* is estimated from the *Kow*, another source of uncertainty will be added to modeled air concentrations. The Panel recommended that EPA should define whether the *Koc* will be estimated from the *Kow*, and by what method, or if literature values will be used.

The Panel suggested that it was possible to assign confidence intervals to the regression to incorporate the uncertainty associated with the measurements used to generate the flux values. These intervals would provide a high and low range of likely values and therefore address the Agency's concerns that the model would under-predict the 24-hour exposure for some compounds. For example, Johnson *et al.* (1995) describe a method for evaluating the quality of physicochemical property data available in the literature or in registrant submitted data. In addition, the Panel recommended that a sensitivity analysis of the terms within the model would be useful, perhaps breaking the regression equation into pieces rather than having everything lumped together. A further suggestion from the Panel for using the Woodrow *et al.* (1997) approach would be to set a receptor location next to the field (*i.e.*, 2-5 meters) and an air concentration of concern estimated from the toxicity data. From this information a maximum flux value could be calculated that would be needed to generate this concentration of concern. Flux values independently generated from the Woodrow model, including confidence intervals, could then be compared with the maximum flux value determined from the air concentration of concern for screening purposes (see also the Vapor Hazard Ratio (VHR) discussion in Topic C). One caveat with respect to the Woodrow model is that some chemicals are applied in such a way that the first 24-hours after application may not include the period of maximum flux. For example, soil incorporated pesticides need time to diffuse to the soil surface or pesticides broadcast as granules into rice fields must dissolve before maximum flux from the water surface can occur. In these exceptional cases, the second or subsequent 24-hour period may contain the period(s) of maximum flux rather than the first 24-hour period.

Panel Response to Question 2b

Major Recommendations/Findings

The Panel agreed that the concept of coupling a fate and transport model such as PRZM or PEARL to predict fluxes, with a model such as the Pesticide Exposure Risk for Fumigants (PERFUM) to estimate air concentrations at different distances from the field is sound as a Tier II, Option B modeling approach for identifying volatile chemicals of concern within the confines of evaluating pesticide volatilization in treated fields (excluding spray drift).. However, the Panel

also suggested that new insights might be gained by conducting the proposed Tier II process in reverse order: use a dispersion model (*e.g.*, Screen3, ICS3, or PERFUM) to establish a maximum acceptable flux that will not produce a concentration of concern at a given receptor location and then use either a Tier I or Tier II screening procedure to establish a maximum acceptable flux estimate for the specific compound. The Panel suggested that the use of the Pesticide Emissions Model (PEM) (Scholtz *et al.*, 2002 a, b) be considered as an alternative to the use of PRZM, as this model was created to describe processes controlling volatilization.

The Panel recommended that novel technologies (sensors or rapid samplers) be explored to achieve higher temporal resolution in the concentration datasets for flux measurements. Innovative methods to characterize gas and particle-phase concentrations during flux measurements and downwind air sampling should be encouraged. For example, the Agency might consider applying other methods for flux estimates, such as EPA method OTM-10 that applies remote sensing techniques. The Panel noted that whatever method is considered, each will have different uncertainties and sensitivities to measured parameters.

The Panel offered several recommendations and suggestions regarding validation and further development of flux models.

1. The Panel stated that rather than basing volatile flux prediction models on back-calculation methods, such models should be validated with direct field measurements of flux under different cropping patterns, application techniques, rates, and frequency, and in different geographic regions. Only once the flux model is validated is the use of multi-year/multi-climate zone meteorological datasets appropriate.

   The Panel concluded that the flux model evaluation presented in the background document is not sufficient to validate the proposed flux models, *i.e.*, PRZM or PEARL. Both models appear to over-predict the "observed" field fluxes. The Panel stated that the "observed" fluxes were not accurate enough or represented an insufficiently extensive database to show that the models performed well.

   For example, in some cases the models, PRZM and PEARL, used within the Agency's examples (Table 5 of the Agency background document, p. 47) predicted roughly twice the measured air concentration, while in others it was as great as seven-times the measured concentration. One possible explanation for such deviations is that the measured data used for comparison were not based on actual source volatilization flux data, but on a back-calculation of source volatilization fluxes that required an air dispersion model to estimate concentrations away from the application site. The model predictions presented for PRZM and PEARL also included estimations of temperature fluctuations as well as other meteorological conditions explained by the EPA experts.

   The model should first be validated with field data that reflects actual experimental conditions before it is evaluated for efficacy and ruggedness (with averaged data). Only then can the predictive capability of the model be accurately assessed. The data used in the Agency's examples were projecting a protective model, but they were too imprecise for an evaluation of the model's validity. The Panel emphasized that the use of actual field flux data to evaluate Tier II models would be paramount in assessing the accuracy

and reliability of the model's predictive capabilities. To that end, the Panel recommended that additional field studies be conducted because those presented in the Agency's background document did not demonstrate that the model could accurately predict vapor phase concentrations.

The Panel made a number of further recommendations related to this general issue of validating evaporation and dispersion models.

a. The evaluation of the flux models should be handled separately from the risk assessment. Flux models using probability meteorology would involve a wide range of atmospheric concentrations; thus, adding unrealistic variability to the surface flux predictions. Therefore, it is important first to understand the model, assure that it predicts known conditions accurately, and then add a realistic level of variability as input to the model to ensure a conservative risk assessment.

b. The model results should be compared to a number of actual field flux measurements, preferably obtained with multiple field flux measurement methods, in order to be proven effective. For example, direct flux measurements, including eddy accumulation as well as indirect methods, such as flux-gradient relationships, should be used in addition to the Gaussian plume inversions used by the Agency. The Panel pointed out that many such studies exist, and some are provided in the list of suggested references.

c. The Panel questioned the use of the Gaussian plume inversion approach for estimating fluxes within an orchard. Trees in an orchard can create coherent eddies organized within the geometry of the orchard, and create a stable sub-canopy layer of air. These effects are not taken into account in the plume models employed to infer fluxes. This is also a problem for atmospheric concentrations estimated from orchard emissions using PERFUM, because the Panel understood that PERFUM is based on the Gaussian plume model and is not adapted to simulate dispersion and transport within plant canopies.

d. The Panel expressed concern that the uncertainty associated with physicochemical properties, such as the *Kow*, soil half-life, and photodegradation, are not incorporated into the current modeling efforts. The Panel recommended that the Agency perform sensitivity analyses to determine the factors (input data and model parameters) that are most important in predicting the flux, and then the impact of uncertainty in these inputs should be used to evaluate the range of fluxes predicted by the model. Flux estimates, even for a given day of meteorological conditions, can be computed as a probability distribution.

e. Flux model evaluations should include situations involving both soil and vegetation sources from soil and vegetation application of pesticides.

f. The Panel recommended that more frequent time point measurement of flux rates should be taken immediately after application, *i.e.,* hourly flux rates. Hourly flux

estimates should be considered for the following reasons: 1) volatilization rates tend to be higher in the hours just after application (*e.g.,* 2-fold as shown in Table C-1) than the daily average, 2) day/night changes in surface temperatures can lead to a substantial difference in surface temperature, thus in vapor pressures, and thus, volatilization rates, and 3) conditions of high atmospheric stability, typically at night, can lead to atmospheric concentrations that are much higher than the daytime average. The sensitivity of the more technologically-advanced mass spectrometers should be enough to measure the levels that would be found at very short sample durations, especially because those initial samples are taken at a time when the airborne concentrations are apt to be the highest.

g. In addition, the Panel indicated that downwind concentration data should also be collected during the field validations of the flux model in order to validate a coupled flux/dispersion model approach for semi-volatile pesticides. While dispersion models have been field-validated for fumigants, they have not been field-validated for semi-volatile pesticides or in other soil types or crop scenarios. Because of their high volatility, fumigant vapors tend to remain airborne for longer periods than semi-volatile pesticides, which tend to be removed from the air mass by condensation or adsorption on downwind air particles, soil, or foliage surfaces. By absorption onto particles and potentially re-volatizing, semi-volatile pesticides with higher *Kows* (*i.e.*, log *Kow* greater than four) have a different fate than fumigants, may have a longer persistence in the environment, and may be transported into homes where the pesticides may reside in house dust (Harnly et al, 2009).

2. Volatilization flux prediction models should include pesticide degradation products. For example, photodecomposition is important to include because it is generally a "loss" term. However, transformation reactions may also be a source of more toxic chemicals, *i.e.*, oxones (oxygen analogs of many organophosphorus pesticides) (Harnly *et al.*, 2005).

The Panel stated firmly that models used to predict the atmospheric concentration of a pesticide should include enough terms to make the predictions act as reasonable surrogates of the measured concentrations. This includes terms that both add to the vapor phase concentration and those that decrease vapor phase concentration (*i.e.,* reduce the parent compound). If the model does not include subtraction terms it will not accurately follow the progression of the flux and is likely to significantly over predict the vapor phase concentration. This more sophisticated Tier II model should be used to evaluate pesticides once they have been screened at Tier I, but any advanced model should include photodegradation as part of the modeling process. Many of the newer pesticides are photo-labile. For example, pyrethorioids often decay rapidly even once collected from field samples. Much of this degradation can be attributed to photodegradation, reinforcing the need for inclusion of photodegradation terms in any model used as a Tier II assessment tool. A photodegradation term will represent the extent to which the vapor phase concentration of the pesticide in the atmosphere is reduced by photoloysis (although not to zero). Existence of this term in the model will help to differentiate the more photo-labile compounds from others that may have a similar vapor pressure, but do not undergo photodegradation.

utilized in the flux modeling. The Panel stressed that the Agency should be more attentive to the physics of the models being tested.

7. The Panel suggested that PEM (Scholtz *et al.*, 2002a, b) would be a reasonable alternative to the use of PRZM or PEARL, as this model was designed to model the behavior of the pesticide into the ground rather than release to vapor, the release to vapor is almost the discard process, the "1 - N term." While a precise model should be able to utilize all calculated compartments, these models (PRZM and PEARL) focus on the soil compartments and therefore potentially over-emphasizes the fraction retained in the soil. Those assumptions will then cause an underestimation of the fractions released as vapor. The need for accurate volatilization flux data will be paramount in evaluating the validity of the proposed model.

8. The Panel also suggested that EPA hold scientific workshops or conferences to bring together the scientific community to aid in the assessment of proposed models and improvements (if necessary), and eventually, the validation of these flux models. Panel members volunteered to help in this endeavor.

9. And finally, the Panel suggested that the Agency consider developing a model of multiple application events in the same region/air shed. In that regard, the Panel made the following comments and recommendations described below.

    a. The Panel agreed that the Tier II models used by the Agency to estimate volatilization flux and air concentrations should focus first on single applications. However, some panelists indicated that the impact of applications on multiple surrounding fields and/or regional use should eventually be considered. In addition, the presentation from Jacobs Farm during the public comment section also raises concerns regarding re-volatilization of deposited pesticides (repeated cycles of volatilization, transportation, and re-deposition of applied pesticides), especially during fog events. Such re-volatilization processes are not considered within in the current modeling efforts.

    b. In addition, the Panel noted that to derive the greatest benefit from the downwind transport and dispersion models, they should be applicable to modeling air concentrations from multiple applications of the same pesticide in a locale, air shed, or air basin. An example of what could be done for fumigants and semi-volatile pesticides is available in a published study on methyl bromide volatilization from several treated fields in the Salinas Valley, CA (Honaganahalli and Seiber, 2000).

    c. The Panel suggested that the impact of crop management practices such as irrigation, tilling, mulching, and burning of fields may have a potential to increase volatilization. These practices and their effects on pesticide volatilization should also be considered.

Terminology Corrections in Agency's Background Document

The following terminology corrections in the Agency's background document were provided by one Panelist.

1. The following text from page 19 describing flux measurement methodology should be edited for accuracy.

"Flux studies also are typically designed to allow for the generalization of results using a computer simulation air model. More accompanying information is generally collected in these studies including meteorology at differing heights typically with thermo anemometers to provide high resolution information about environmental conditions which are important in understanding the movement of pesticides from the treated area and reducing the uncertainty associated with the flux calculations."

a. Flux measurements are typically designed to measure the flux, not the concentration, of a trace gas. One can infer fluxes from an array of concentration measurements, such as has been described here, but this is not what most micrometeorologists would call a flux study. See Dabberdt *et al.* (1993) for a concise description of flux measurement methods.

b. In comparison to sonic anemometers, thermo anemometers are not the most sophisticated tool to use to measure turbulent wind associated with turbulent transport. Thermo anemometers are not used to reduce uncertainty in the calculations. The Agency's wording reflects a weak understanding of the research underlying these transport mechanisms,

2. The following text from page 20 needs to be edited.

"There are a number of recognized common flux methods in the peer-reviewed literature. Some of the common methods are the Indirect or Back-calculation Method, the Aerodynamic Method (Majewski *et al.*, 1993), and the Integrated Horizontal Flux Method (Wilson and Shum, 1992)."

There are additional flux methods that should be considered by the Agency, for example, eddy covariance. The Agency should review Dabberdt (1993) and modify this section as they see fit after reviewing the available literature.

TOPIC B: Toxicological Assessment Issues

As the understanding of the state-of the science in inhalation toxicology has evolved, so has the Agency's approach to conducting inhalation hazard and risk assessments. This evolution has seen the Agency move from converting oral doses to inhalation concentrations to using the RfC methodology and/or physiologically-based pharmacokinetic (PBPK) models. As OPP continues to work on refining the risk assessment paradigm, the Agency is seeking the SAP's input on a number of key factors. They include the use of oral toxicity studies when inhalation studies are not available and the use of aerosol inhalation toxicity studies to represent toxicity to vapors of

the same chemical. Specifically, the Agency identified the following issues for the Panel to consider:

B.1) The analysis conducted by the Agency indicates that, in general, oral toxicity studies may not accurately represent the full spectrum of toxic effects that may occur as a result of inhalation exposure. The analysis also indicates that - unless the same endpoints are identified through both routes of exposure - oral toxicity studies frequently underestimate toxicity by the inhalation route. The Agency has not been able to discern any patterns in this under/over estimation. *Please comment on any potential patterns that the Agency has not identified.*

Panel Response

Route-to-Route Extrapolation Issues

The Panel noted that EPA placed significant emphasis in the background document on the ability to use toxicological data generated from oral exposures to establish Inhalation Equivalent Concentrations (IECs) even though they recognized that such a strategy is seldom valid. Nonetheless, the Panel evaluated this approach and recommended that if such extrapolation is considered that the guidelines as outlined in *Principles of Route-to-Route Extrapolation for Risk Assessment* should be followed (Gerrity and Henry, 1990) and only for those pesticides that meet the criteria noted below. One Panelist commented that this book was an outgrowth of a workshop sponsored by the EPA in March 1990. Many concepts and issues raised in this book were also later addressed by Rennen et al. (2004), with essentially the same conclusions being reached. Basically, the only chemicals that are candidates for route-to-route extrapolation are those having no portal of entry effects and those whose kinetic behavior is independent of exposure route. The summary report section of Gerrity and Henry (1990) provides a decision tree for assessing how the information available for a given chemical can be used to identify the path forward and ascertain if sufficient data are available to attempt any route-to-route extrapolation.

Review of the available literature evaluating route-to-route extrapolation indicates that, for the most part, there is no pattern of consistency in the results when oral toxicity data are used to model inhalation toxicity for most chemicals. Extrapolation results appear to be somewhat random, with oral to inhalation extrapolation resulting in either over-estimation or under-estimation of inhalation toxicity depending upon the specific model approach used. The only chemical class in which there appears to be some consistency is systemic toxicants that have long half-lives in the body.

The Panel concluded that route-to-route extrapolations using oral toxicity data to assess toxicity via the inhalation route is only scientifically justified, if a validated PBPK model is available or if the pesticide falls into Category 3 chemicals according to the Agency's Inhalation Reference Concentration (RfC) classification scheme (*i.e.*, those gases/vapors that cause systemic effects and not point-of-entry effects) (EPA, 1994) and the following criteria are also met.

a. The toxicological effect of concern is systemic for both entry routes and this effect is independent of route of exposure.

b. The first pass effects in the liver for oral exposure and in the respiratory tract for inhalation exposure are minimal to nonexistent or, if there is some first pass effect, the metabolism following exposure is the same for both exposure routes.

c. The chemical will not be chemically modified by the gastrointestinal bacteria or enzymes or by the acidic environment in the stomach differentially than it would be in the more neutral to slightly basic environment of respiratory tract fluids. Pesticide stability in gastric fluid should be of primary concern in considering the use of oral exposure data. If the compound is not stable in gastric fluid, the toxicological data on oral dosing would be of little to no value in estimating any inhalation toxicity.

d. The absorption efficiency for oral and inhalation exposure must either be identical or known, so that accurate values may be incorporated into any model. The absorption efficiency for oral and inhalation exposure must either be identical or known, so that accurate dose values may be incorporated into any model; the use of a default value of 1 for absorption is not justifiable in the absence of any data. Furthermore, the absorption cannot be differentially influenced by a toxic response unless this response is the same via both routes and/or is influenced by relatively the same extent via both routes.

Even when the above criteria are met, the Panel recommended an additional UF of 10 (as an example) for the final extrapolation for inhalation from oral data. The Panel stated that uncertainty factors are not a replacement for more accurate modeling and additional data from more inhalation toxicity studies. The Panel provided a detailed discussion as to why it is scientifically justifiable to request additional inhalation toxicity data. Discussions and data presented during the meeting clearly show that repeated exposures to pesticides are occurring. Based on this discussion, the Panel strongly recommended that the Agency obtain additional inhalation toxicity data if such data are not available and if the vapor form of the pesticide does not meet the criteria for route-to-route extrapolation as described above.

Use of *In Vitro* Studies

The Panel noted that some of the problems associated with route-to-route extrapolation from oral toxicity studies to inhalation toxicity studies might be evaluated by simple *in vitro* studies, such as solubility and stability in simulated gut or lung fluid (as discussed in more detail below), or by consideration of the chemical structure of the pesticide and using structural activity relationships. For example a pesticide may be very stable in a synthetic lung fluid, which has a much higher pH than a human gastric fluid. Pesticide instability in a gastric fluid would therefore suggest a much lower toxicity through ingestion than inhalation.

Solubility of the inhaled chemical within lung fluid is the first step in the toxicological process and can be modeled using a synthetic lung fluid (Dennis *et. al.*, 1982; Eidson and Griffith, 1984). This parameter may be assessed as part of a screening process. Similarly, synthetic gastric fluids may be used as a screen for considering not just bio-solubility, but also pesticide stability through the ingestion pathway. Both of these solubility tests can also be used to screen

particulates as well. Finally, if a route-to-route exposure model for inhalation of vapors is to be evaluated, then a more appropriate dosing model might be injection rather than ingestion.

The Panel provided a hierarchy of *in vitro* models that could be used for assessing bioavailability in humans of any pesticide. The overall delivered dose can be approximated by animal exposure studies. Cell culture experiments can potentially be used to predict target organ processes. Dependent on dose, they can be used to evaluate cell death, mutation or, at lowest dosing levels, metabolism, but not solubility or even stability because the fluids used to stabilize the cells do not always accurately represent the fluids interacting with the target organ. The next level in the hierarchy would be determining the bioaccessibility of the pesticide. In these studies, the soluble component must pass through a semi-permeable membrane that would approximate the actual target tissue of interest. The final level would be creating an estimate of the biosolubility of the tested compound. This can be done using simulated biological fluids. Use of simulated biological fluids has the potential to correct for interspecies differences because the biological fluid can be created using a formulation (or recipe) based on ratios of constituents that most closely approximate that occurring in humans or animals used in exposure testing above. For the bioaccessibility and biosolubility *in vitro* models, the physiological endpoint being approximated is dose delivered to the next compartment, generally the blood.

Equation for IEC

The EPA background document presents an equation for calculating an IEC that attempts to take into account various factors, such as minute ventilation, animal body weight, exposure duration, absorption efficiency, etc.; however, the Panel noted two problems with this equation. First, species differences in surface area/body weight are not accounted for, so that the equation needs to be modified. In cases where route-to-route extrapolation may be justified, *i.e.*, pesticides that fit into EPA's RfC Category 3, it would be better to adjust the animal oral dose to a human equivalent oral dose (*i.e.,* adjustment based on body weight raised to the ¾ power (EPA, 2005) before further adjusting this value to an IEC for humans. The Panel stressed that the use of an IEC equation should be restricted to cases where the vapor falls into EPA's RfC Category 3 and also meets the four extrapolation criteria listed earlier.

NOAELs vs. BMDs

The EPA background document mainly focuses on the use of No Observed Adverse Effect Levels (NOAELs) and Lowest Observed Adverse Effect Levels (LOAELs) as bases for calculating IECs or Human Equivalent Concentrations (HECs). The Panel noted that the value of the NOAEL or LOAEL is sensitive to the nature of the experimental design used to conduct the study and, therefore, recommended that the Agency consider Benchmark Dose (BMD) analysis when concentration-response data are available and are amenable to modeling. The Panel added that because BMDs can be established for various percentages of effects, the Agency would have various regulatory management options to consider that reflect magnitude of risk. The Agency could then select the option(s) that most closely align with their specific risk management goals.

Use of Haber's Law in Duration of Exposure Adjustments

The Panel stated there were several problems with the way in which EPA used Haber's Law (or Rule), in making adjustments for the duration of exposure when calculating HEC's from repeated exposure inhalation toxicity studies. As stated on p. 59-60 of the Agency background document, "Thus, application of this procedure provides an automatic margin of protectiveness for chemicals, for which C_{max} alone may be appropriate, and it reflects the maximum dose for agents for which total or cumulative dose is the appropriate measure."

First, Haber's Law has been shown not to be applicable to a great number of toxicological responses. Miller and colleagues (2000) showed that this Law is merely a special case of the generalized power law family. Basically, one arrives at Haber's Law when $\alpha = 1$ and $\beta = 1$ in the generalized power law equation, given as $C^{\alpha} x T^{\beta} = k$, where C is exposure concentration, T is the duration of the exposure and k is a fixed level of effect.

Second, whether the use of Haber's Law provides an automatic margin of protectiveness is entirely dependent upon the values of α and β in the power law family of curves. Miller *et al.* (2000) illustrated these differences (see Figure 9 in this paper). Figure 1 below is a reproduction of Figure 9 in Miller *et al.* (2000). For example, when $\alpha > 1$ and $\beta < 1$, the use of Haber's Law to extrapolate from high to low level exposures actually results in an under prediction of risk (see Case C, Figure 1). In contrast, the Panel indicated that the Agency is assuming that $\alpha > 1$ and $\beta > 1$, *i.e.*, Case D, Figure 1. During her presentation at the meeting, Ms. Annie Jarabek, EPA, Office of Research and Development (ORD), National Center for Environmental Assessment (NCEA), illustrated the issue of conservatism dependence as a function of where one is on the rectangular hyperbola relating concentration and time to a fixed level of biological response.

One Panel member noted that NCEA is in the process of developing software that can fit a variety of generalized power law family C x T models. These models would likely be of great interest to OPP, particularly those that relate to acute exposure modeling and those that account for $C^N x T$, where N captures the ratio of α and β (see EPA, 2008; page 10, document on the ten Berge models).

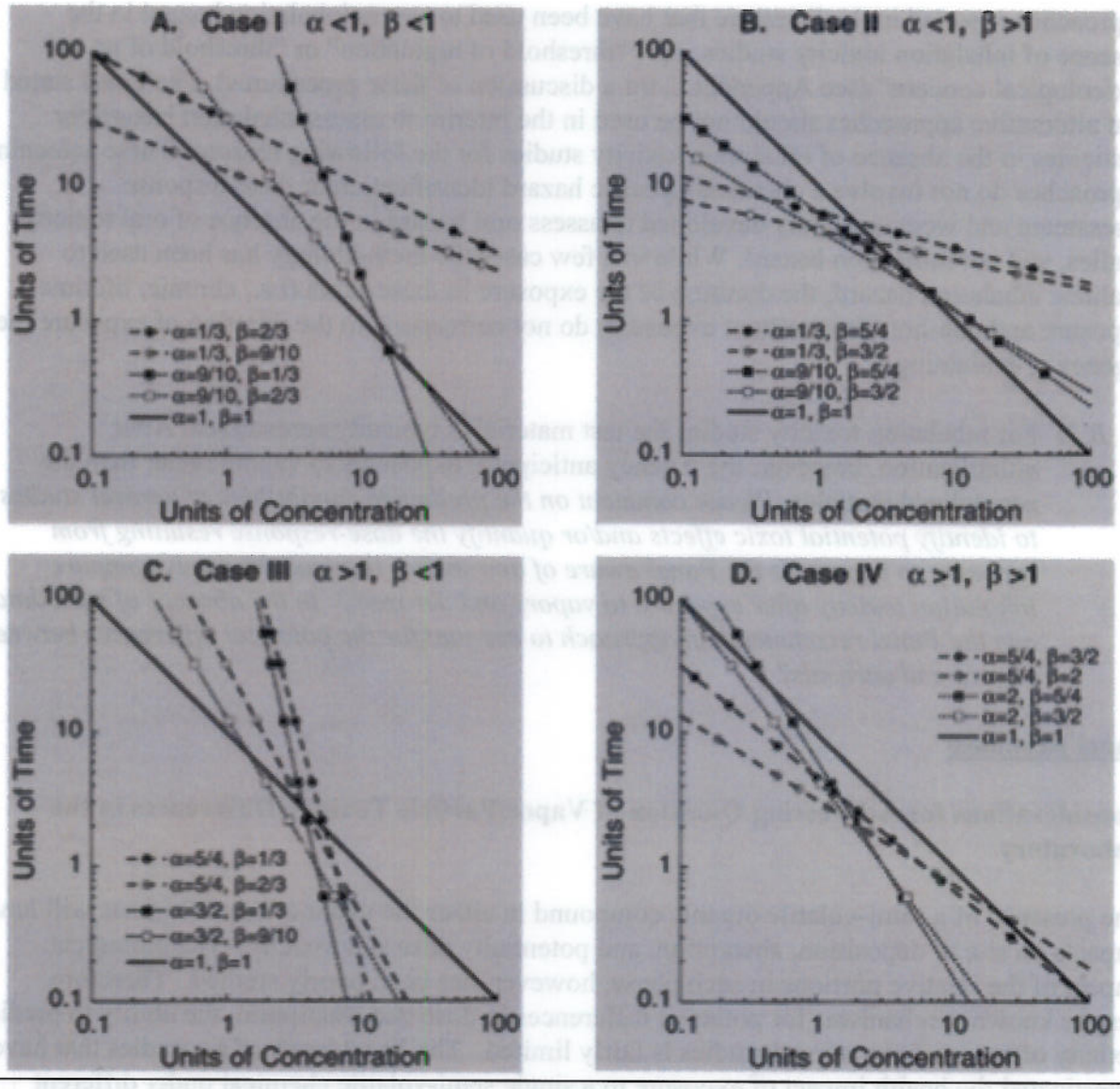

Figure 1. Log time-log concentration plots for the general power law family, $C^{\alpha} x t^{\beta} = k$. The panels depict the four combination of α and β. Included for reference is the line of identity (Haber's rule) corresponding to $\alpha - \beta = 1$. Here k is fixed at 10 for all plots. Reproduced from Figure 9 in Miller *et al.* (2000), with permission.

B.2) For a significant number of conventional pesticides, inhalation toxicity studies are not available. *Please comment on the scientific strengths and weaknesses of available approaches that may be used in the interim to assess inhalation hazard in the absence of inhalation toxicity studies.*

Panel Response

Overall, the Panel strongly recommended that the Agency conduct inhalation toxicity studies to adequately assess inhalation hazard. One Panel member provided a summary of alternative

approaches reported in the literature that have been used to assess inhalation hazard in the absence of inhalation toxicity studies, *e.g.*, "threshold of regulation" or "threshold of no toxicological concern" (see Appendix C for a discussion of these procedures). The Panel stated that alternative approaches should not be used in the interim to assess inhalation hazard for pesticides in the absence of inhalation toxicity studies for the following reasons. These screening approaches do not involve a chemical-specific hazard identification or dose-response assessment and were originally developed to assess oral hazard in the absence of oral toxicity studies, and not inhalation hazard. While in a few cases the methodology has been used to evaluate inhalation hazard, the duration of the exposure in these cases (*i.e.*, chronic, lifetime exposure and one-hour intermittent exposure) do not correspond to the duration of exposure the Agency is evaluating.

B.3) For inhalation toxicity studies the test material is typically aerosolized. After volatilization, however, the Agency anticipates exposures to vapors rather than the aerosolized particles. *Please comment on the predictive capabilities of aerosol studies to identify potential toxic effects and/or quantify the dose-response resulting from exposure to vapors. Is the Panel aware of any studies that quantitatively compare inhalation toxicity after exposure to vapors and aerosols? In the absence of such data, can the Panel recommend an approach to account for the potential differences between vapors and aerosols?*

Panel Response

Considerations for Addressing Question of Vapor/Particle Toxicity Differences in the Laboratory

The presence of a semi-volatile organic compound in either the vapor or particle phase will have impacts on site of deposition, absorption, and potentially dose and toxicity. The biological impact of the relative portions in each phase, however, has been poorly studied. Therefore despite known mechanisms for potential differences in dose and absorption, the ability to predict toxicity of vapors from aerosol studies is fairly limited. The Panel knew of no studies that have investigated the health impact of exposure to a single semi-volatile chemical under different phases. Some studies with mixtures have utilized techniques to either remove the particulate phase by filtration or the vapor phase by using a denuder to study the role of those materials independently (McDonald *et al.*, 2007). In many cases, the removal of the particulate phase of the mixture has not resulted in biological effects that differ from those obtained with the total mixture, especially for systemic effects. These mixture studies, however, may not be appropriate to answer questions related to a single component study. The Panel stated that there remain fundamental questions (beyond just the deposition site) related to the relative toxicity of vapors and particles. These must be considered as adding uncertainty when attempting to predict biological effects from exposure to the vapor versus particulate form of any given pesticide.

In the case of semi-volatile organic compounds (SVOC), chemicals can exist in the gas and particle phase simultaneously. The relative proportion in either phase will depend on concentration, temperature, humidity, and other particulate matter in the air. Volatile flux from crops will result in concentrations that are substantially below the saturation vapor pressure of

that imparts conservative calculations (*i.e.*, for the range cited here, one would use 50%) and then apportion the uptake across the three major respiratory tract regions. For example, if most of the vapor is taken up in the ET region and some is delivered to the TB region but very little reaches the alveolar region, then the total uptake might be apportioned as 40% ET and 10% TB.

4. Use the appropriate ventilation data for the animals in the pesticide aerosol study and compute what vapor phase exposure would be needed to yield the same value of the dose metric as was computed in Step 2. One may well find that the region for uptake is different than the region where the pesticide aerosol is primarily deposited. However, since the cells lining the non-olfactory epithelia in the ET and TB regions are reasonably similar (Miller *et al.*, 2010), a mass per unit surface area dose metric is likely to still be an acceptable metric.
5. Next, make similar calculations for humans as was done in Step 5 to see what levels humans would have to be exposed to for what periods of time in order to achieve the same numerical value of the dose metric calculated for the animals.
6. Now move forward with RfC or HEC calculations as inputs to the assessment of risk.

The Panel noted that this procedure is a possible way to obtain information on the vapor form when only aerosol exposure studies are conducted. The modeling approach is intended to help provide some interpretation of the findings from the aerosol study in assessing potential effects from exposure to the vapor. The Panel briefly discussed this procedure and thought it was reasonable; however, they recommended that EPA assess it further to determine its ultimate utility.

ADDITIONAL DISCUSSIONS ON INHALATION TOXICITY

The Panel discussed various topics that were an outgrowth of the charge questions. The order of the topics is not in order of priority.

Appropriate Averaging Times and Sampling Devices for Field Measurements

Currently, measurements of pesticide levels collected from fields where crops have been treated with pesticides are based upon 24-hour samples. During the public comment period, Dr. Susan Kegley of the Pesticide Research Institute presented data showing significant variability in air concentrations of volatile pesticides over periods of time shorter than 24-hours. Many individuals and families live either alongside of crop fields or even within orchards. Thus, there are significant opportunities for both children and adults to be repeatedly exposed to volatilized pesticides. Moreover, given the large variability in exposure levels in the first hours following pesticide application and then the subsequent temporal variability, the Panel recommended that the Agency collect exposure data with shorter collection times than 24-hours and to use these data in health effects evaluations. For research purposes, samples collected over 2- to 4-hour periods will likely be needed to assess the variability of the pesticide concentration in the air soon after pesticide application and over the next few days.

Appropriate sampling devices for the above studies would be able to separate the vapor form from the particulate form of the pesticide, or at a minimum ensure that both the vapor and particulate portion of the atmosphere are included. This can be accomplished with denuders and filters, or a combination of filters succeeded by vapor sorbents. Samplers with automatic switching manifolds to permit high frequency sample switching are commercially available. Given the activities in which workers must engage, there is a strong likelihood that individuals surrounding the fields and the workers themselves are exposed repeatedly to both respirable pesticide particles and vapors. The Panel recommended that the Agency collect exposure data for both, so that the relative contribution of each to overall exposure may be assessed.

Protocols for Inhalation Toxicity Studies

The Panel recommended that inhalation toxicity studies should be conducted with an exposure duration of up to 90 days. For example, an inhalation toxicity study conducted at 1, 7, 14, 28, and 90 days of exposure would generate an adequate database to address both acute and subchronic exposures. The length of daily exposure may be guided by what is seen in monitoring studies when collection times shorter than 24-hours are used. These timeframes are reflective of the duration of human exposure to respirable particles and vapors via inhalation. The Panel recommended that the length of exposure per day should be guided by new field studies that are conducted to assess the variability in air concentration of the pesticide particles and vapors.

The earlier time points (*i.e.,* 1, 7, 14, and 28 days) would tend to capture the initial application period for the pesticide, any potential reapplications due to weather conditions, as well as additional weekly applications of a pesticide. The Panel indicated that the 90-day time point would provide a link for using a subchronic study to assess potential effects due to chronic exposure effects, with perhaps an UF added to adjust for not having chronic exposure data. The Panel pointed out that results of the subchronic studies may guide the potential requirement of chronic studies that intend to investigate long term effects such as cancer..

In addition, the studies should consider the likely types of biological effects that might be expected for the given type of pesticide. The Panel pointed out that the Agency should consider that new toxicity studies take advantage of the scientific advances in understanding inhalation toxicity and exposure assessment that have evolved over the past 30 years.

Overall, the appropriate approach for the inhalation study will be one that, to the extent possible, mimics human exposure conditions. The Panel noted that new vapor inhalation studies for semi-volatile compounds may be limited, perhaps, to cases where there is a predicted level of flux above a certain threshold. This may be determined, as discussed above, through flux modeling derived through fate/transport studies.

Uncertainty Factors for Quality of the Database and What Constitutes a Minimum Database

Other EPA offices (*e.g.,* Office of Water, Office of Research and Development, Office of Air and Radiation) and regulatory programs have established criteria for what constitutes a minimum

database for chronic exposure that must be available so that a health assessment, an inhalation RfC for chronic exposure, an oral RfD, etc. can be determined (*e.g.*, see EPA, 1994). The Panel recommends that EPA establish such criteria for short-term studies (*e.g.*, 1, 7, 14, 28 days) and that they use an additional UF of 10, if only a minimum database is available for their assessment.

Moving Toward a Cumulative or Total Risk Assessment

The Agency's background document notes that potential pesticide exposures can occur from three types of scenarios: during application directly, due to application drift and due to volatilization following application. Furthermore, exposure may be to respirable particles, or vapors, or both. While the background document is only concerned with volatilization of pesticides following application, the Panel noted that a broader view is going to be needed for the future. Therefore, the Panel recommended that total exposure be assessed to more fully encompass all types of inhalation exposures for the risk assessment process. For example, the Panel acknowledged the difficult situation that was occurring to crops on the Jacobs Farm (oral comments provided by Mr. Larry Jacobs, Pescadero, CA and owner of Jacobs Farm). They concluded that the situation on Jacobs Farm demonstrates that there is a problem with volatilization and possibly re-entrainment of particulate pesticides. If this situation is due to such transport processes, then individuals should also experience pesticide exposures from volatilized pesticides and, possibly, respirable particles.

The Panel suggested that the Agency consider the hazard quotient (HQ) or similar approach to assess risk from each of the types of exposure that contribute to the total potential exposure following application of pesticides because, at a minimum, workers are exposed to respirable particles and vapors both during direct application and drift. Moreover, those living close to fields where pesticides are applied are likely to receive exposure from more than the volatilization route. Hazard quotients from different pathways (or from different pesticides) could be added together to calculate an overall hazard index [HI]. If the resulting HQ or HI is $\leq$ 1, then adverse health effects would not be expected. If the HQ or HI is slightly > 1, then it would not necessarily mean that health effects would occur but that further evaluation was warranted. If the HQ or HI is significantly > 1, then it would indicate health effects would be likely to occur. The hazard quotient would seem to offer a better alternative than a MOE approach to aggregate risk. Hazard indices for pesticides with the same mode of action could be used for assessing cumulative risk from inhalation exposure to multiple pesticides.

TOPIC C: Risk Assessment Issues

The Agency discussed its methodology for combining the exposure estimation methodologies and inhalation toxicological approaches to estimate postapplication bystander inhalation risks resulting from field volatilization of conventional pesticides. In estimating postapplication bystander inhalation risks, there are a few principles that should be followed: (1) properly match the duration of the exposure with a proper toxicity study of comparable duration; (2) both dissipation of air concentrations around a treated field as well as when retreatment of the field may occur, need to be considered; and (3) clearly define the uncertainties and limitations of this

type of assessment. The Agency has identified the following issues for the Panel to consider with respect to estimating postapplication bystander inhalation risks:

Please comment on the strengths and limitations of the Agency's use of the empirical and modeled air concentrations in the provided risk assessment case study. Does the Panel agree that the postapplication bystander inhalation risk estimate case study appropriately matches the duration of the exposure with the proper toxicological study of the same duration? Please comment on the scientific strengths and weaknesses of conclusions and characterization regarding the estimated risks presented in the case study.

Panel Response

C.1) Please comment on the strengths and limitations of the Agency's use of the empirical and modeled air concentrations in the provided risk assessment case study.

The strengths and weaknesses of the Woodrow empirical model are much the same as the Panel discussed above in Topic A, Question 2a. The main strength of this model is its basis in multiple studies over a wide range of vapor pressures; a secondary strength is that its results are in the range of the results of the air concentrations estimated by more sophisticated modeled air concentrations. The limitations of the model are that it is based on a limited range of crops, weather, and locations, does not take into account the potential effect of an activity coefficient on vapor pressure, and is applicable only to the first day post-application.

The strengths of the computer-based modeled air concentrations are that they can account for dynamic changes in post-application conditions and residue history. Their weakness is the limited knowledge that users have of the internal components of these models, the concern that the components do not model evaporation from foliage as well as they model evaporation from soil, and that the particular analyses presented to the Panel inappropriately decoupled the variance of the flux from the variance of dispersion.

Discussion of the Tier IIA Model (Woodrow *et al.* Model)

Several panelists again suggested that the accuracy of the Tier IIA, Woodrow *et al.* (2007) model's estimation of airborne pesticides concentrations could be more precise by adding more variables (see earlier discussion under Topic A, Charge Question 2a. The Woodrow model's basic structure of a log-log regression lends itself to multiple regression analysis. Two variables of initial interest would be the influence of the pesticide's application rate and foliage density on flux. Some panelists cautioned that worst-case scenarios could not be easily identified for this model because of the narrow set of conditions that were available and used when the model was originally developed by Woodrow *et al.* (1997).

On the other hand, one Panel member suggested that the utility of the Woodrow model could be expanded by using its predicted 24-hour flux rate in conjunction with a mass balance to derive a per hour flux rate. One such expansion could be derived by assuming that the flux rate decreases exponentially with time, as depicted in Equation C1, where τ is the exponential rate constant.

most vapors. Therefore, in most cases, re-equilibration will be defined not by concentration, but by other factors such as the presence of other particulate matter, and conditions of temperature and humidity. These other factors can be measured, and incorporated into models using gas/particle partitioning models (see Odum *et al*, 1996; Pankow *et al*., 1994). An additional exposure estimation concern includes the flux over time of the pesticides.

Depending on the vapor pressure of the compound studied, it is indeed plausible that significant amounts of vapors existed in the laboratory studies that were conducted to determine pesticide toxicity. The gas/vapor partitioning models cited above can be used to predict the fraction of compound in the gas and particle phase at a given environmental condition and concentration. For a simple case where only one compound is present, this model can utilize first principles. However, it should be noted that for a semi-volatile material where the aerosol was sampled with a filter, one could obtain inaccurate dose estimates due to potential volatilization of vapors from the filter and/or adsorption of vapors onto the filter.

Once actual exposure is more accurately defined, the appropriate exposure scenario can be developed. One issue is the fact that the majority of laboratory inhalation studies were done with aerosolized formulations or powders at high concentrations. These conditions do not represent the true physical form of the pesticide as it exists after volatilization at relatively low concentrations. The toxicologically relevant impact of this is that vapors may be 50-100 % absorbed in the respiratory tract; depending on the reactivity of the material, the vapors may or may not penetrate deep into the respiratory tract prior to removal. Studies with highly reactive and highly soluble vapors in rodents have shown that the biological response is limited to effects in the nasal passages and upper tracheobronchial (TB) airways. Particles may have more or less deposition (and, therefore, dose) than vapors, with the deposition amount and location in the respiratory tract dependent upon the size of the aerosol. Because of the aerosol generation approaches used in the past, the particles in the laboratory studies will likely be 2-3 micrometers and be polydisperse. In this case, the majority of the material will deposit deep into the respiratory tract, and at a much lower fraction than the vapors. Polydispersivity, however, will result in some overlap of deposition sites with those for vapors whose uptake sites can be predicted with reasonable certainty.

An approach to link aerosol data with vapor data would need to make the assumption that the form of the material will not impact absorption once it is removed from the air stream. Once more, the site of deposition would need to be considered, perhaps using currently available modeling approaches for particles and evolving modeling approaches for vapors. In this case, dose relationships between the studies can be established, and responses can be related in a more appropriate way. Once the site of deposition is better understood, another important consideration is the nature and type of biological effects observed. These may be able to be related to the site of deposition for local effects, and to bioavailablity/absorption for systemic effects. For compounds that show high absorption, the vapor and particle components of the aerosol will likely show reasonably similar systemic biological responses following deposition.

Potential Modeling Approach for Using Aerosol Studies to Assess Vapors

Based on the discussion during the meeting, the Panel understood that EPA has 25-40 year old aerosol pesticide studies that might provide some insight into the potential toxicity of the volatilized form. These studies essentially used the "neat" form of the pesticide, *i.e.,* a very high technical grade purity chemical. The Panel suggested a potential approach to examine these studies for useful toxicological information regarding the volatilized form of the pesticide:

1. The Multiple-Path Particle Dosimetry Model (MPPD) should be run for various mass median aerodynamic diameter (MMADs) and geometric standard deviation (GSD) combinations within the interval of MMAD greater than 2-3 μm and a GSD of 2-2.4, to establish variability of the predicted deposition. This will enable the Agency to assess the variability/sensitivity of the results obtained in subsequent steps. For example, if one uses the rat as the experimental animal, the MPPD model can be used with this input data to determine the amount of the pesticide aerosol deposited in the major regions of the respiratory tract (Anjilvel and Asgharian, 1995; National Institute for Public Health and the Environment (RIVM), 2002). The MPPD model is publically available for free and can be downloaded from http://www.ara.com/products/mppd.htm.

   The Panel added that EPA's Regional Deposited Dose Ratio (RDDR) model could be used for other animal species (EPA, 1994). In older aerosol studies, the MMAD and the GSD of the aerosol were not reported; however, the methods used, during the aerosol generation did not create particle distributions with a MMAD greater than 2-3 μm and a GSD of 2-2.4. Lack of reporting these values for these studies, therefore, was not a concern.

2. Because the MPPD model can provide estimates of various dose metrics (*e.g.,* mass per unit surface area, number of particles per alveolus, etc.), the next step is to determine which dose metric best fits or is likely to best correlate with the biological response of interest. For the extrathoracic (ET) region, the total mass deposited per unit surface area .is probably the only dose metric that can currently be calculated. To do this, one needs to use an estimate of ET surface area (see Ménache *et al.,* 1997) and the mass deposited in the ET obtained from running the MPPD model. MPPD provides the TB surface area for the size of the animal studied, but the alveolar surface area currently displayed by MPPD reflects only the surface area of the alveolar ducts. Miller *et al.* (2010) provide an algorithm to estimate the total alveolar surface area.

3. Use air: blood partition coefficients, solubility, Henry's law values, etc. to determine the likely regions of the respiratory tract in which the vapor form of the pesticide will deposit. For example, Overton and Jarabek (1990) show how this information can be used to identify likely respiratory tract regions (*e.g.*, ET and TB, alveolar) where specific gases and vapors will be deposited up following exposure.

   By examining various gas uptake studies published in the literature, the Panel thought that EPA would find that total respiratory tract uptake ranges between 50 to 100 % in laboratory animals. For whatever range is found, use the lower value of the interval, as

Photodegradation rates of pesticide vapors have been studied for several pesticides, (see review by Atkinson *et al.*, 1999). In some cases, photodegradation rates of pesticide vapors are quite significant, such as for those organophosphorus thions (*i.e.*, sulphur analogs) that are converted to oxons. However, the oxons are more toxic than the thions, and thus could contribute significantly to the hazard associated with the vapor during downwind drift. Therefore the chemical product of the photodegradation reaction must also be considered.

3. Volatilization dispersion prediction models should include scenarios with temperature inversions. Temperature inversions are common in some parts of the US whereby an air mass may be trapped and normal dissipation and dilution due to air mixing and ventilation are impeded. Inversions could create the potential for exposures to airborne pesticide concentrations that are higher and for a longer duration of exposure than expected.

   The Panel stressed that monitoring and modeling should be flexible enough to take into account unusual topographical, meteorological, and other environmental features that might affect exposures resulting from pesticide residues in the air. For example, temperature inversions are common in some parts of the United States. Temperature inversions in agricultural valleys or other topography can trap the air mass, and impede normal vapor dissipation due to dilution during air mixing and ventilation. This could create the potential for exposures to airborne pesticides that are higher than expected, and for longer than normal duration. In the San Joaquin Valley of California, an area of very high pesticide use including in the winter, wintertime inversions can lead to ground fog that: (a) traps a cool air mass, (b) modifies dissipation by photolysis and/or wind dilution, and (c) creates a partition phase (pesticide suspended in fog water droplets) that can concentrate some pesticides, aiding their deposition to non-target crop foliage, and potentially changing the airborne composition from one dominated by the vapor form to one that is aerosol-dominated. How processes such as this affect exposures of people to airborne pesticides need to be taken into account in designing monitoring and modeling programs.

4. The Panel recommended expanded pesticide use reporting and a national air monitoring network for pesticides to more accurately assess community exposure.

   The Panel recommended that more expansive pesticide usage data, as well as more regional air pesticide monitoring data, be generated to more accurately predict exposure by the public. For example, Panel members noted that the pesticide use reporting system in California has been extremely useful for research scientists and policy makers to increase the understanding of the environmental fate of pesticides. This type of system could also be used in other regions, especially where volatile or semi-volatile pesticide use is high. A standardized air monitoring network in agricultural regions of the US would also be extremely useful. These data could be used to further validate pesticide emission and atmospheric transport models and to estimate pesticide exposures to communities.

5. The Panel suggested a more careful evaluation of the literature on ambient air monitoring in agricultural communities, *e.g.*, Lee *et al.* (2002), Kollman (2002), as well as field volatilization flux measurements, and modeling, *e.g.*, Raupach *et al.* (1996).

   The Panel recommended that there be a broader review of the volatilization flux measurement literature. Studies exist that can be used to evaluate these models. A rich literature exists concerning flux measurement methodologies, uncertainties, and measurement requirements. For example, scientists such as Ralph Nash, Dwight Glotfelty, Alan Taylor, and William Spencer have carried out studies that discuss in detail the factors that influence the volatilization flux from soil and other surfaces (see "Recommended References"). Other studies report the volatilization flux of pesticides from flooded rice fields as contributors to measured airborne residues of pesticides in the Sacramento Valley, CA (Seiber *et al.*, 1989). Also recommended are papers by Scott Yates (USDA-ARS, Riverside) that include the use of field flux chambers for measuring volatilization in the field. Many of the field volatilization flux papers published before 1995 have been compiled in Majewski and Capel (1995). Rich literature also exists concerning transport within forest canopies. A selection of literature that the Agency might find useful is provided in the "Recommended References" list in the "Reference" section of this report.

   In the introduction of the background document, EPA presented citations to available air monitoring data collected both in population centers of agricultural communities or "ambient" levels and adjacent to fields or "application site" monitoring. Additional summary articles are available (Lee *et al.*, 2002). The California Department of Pesticide Regulations (CDPR) has also summarized near-field and ambient data available as of 2000 (Kollman, 2002; Tables 1-2). The Panel recommended that EPA present summary tables of all of these measured air concentrations for two reasons. First, these levels would be useful in describing the breadth and magnitude of potential public health concern for pesticide volatilization from agricultural fields. Secondly, these levels may be used, at every step in the process, to evaluate air modeling efforts.

6. The Panel recommended that the Agency gain a better understanding of the physics of the models they are proposing for this application. It was not clear whether the Agency was using a variable laminar boundary layer depth that is a function of evapotranspiration, as originally proposed by Jury *et al.*, (1983), or a constant laminar boundary layer depth. The Jury *et al.* (1983) proposal is not physically sound for the purpose used by the Agency. A constant laminar boundary depth layer is more physically realistic (*e.g.*, Panofsky and Dutton, 1984). PRZM appears to use a constant laminar boundary layer depth. The Panel was not yet able to ascertain the treatment of this issue in PEARL. The Agency's background document did not clarify this issue.

   The models proposed (PRZM and PEARL) appear to assume a zero atmospheric mixing ratio and to neglect aerodynamic resistance when estimating fluxes, which should tend towards an over-prediction of the flux. This should be kept in mind when evaluating the models. PRZM documentation described assumptions concerning the aerodynamic resistance, but the use of this resistance in the model was not clear. PEARL documentation was difficult to obtain. Thus it was difficult to evaluate the assumptions

$$\text{flux rate at any time} = \text{initial flux rate H } e^{-t/\vartheta} \qquad \text{Eqn. C1}$$

For example, if the application rate were two pounds per acre (using an "eyeball" average of the application rates in Table 1 of Woodrow *et al.* (1997) and taking into account that 1 kg/ha = 1.03 lb/acre, then the initial residue would be equivalent to an average deposition of 0.22 g/m² across a flat field. For a pesticide with a vapor pressure of 1×10^{-4} mm Hg, the Woodrow model (translated in Equation C2 out of its log-log format) would predict an initial 24-hour flux rate of 0.0032 /m²/hr.[3]

$$\text{Flux}_{day\ 1} \text{ in Woodrow model} = 8.574 \times 10^{6} \times P_{vapor}^{\ 0.85543} \qquad \text{Eqn. C2}$$

One can use Equation C3 to calculate this flux is equivalent to a rate coefficient [ϑ] of 2.3 days or an exponential half-life of 1.6 days (where HL = ϑ H ln2).

$$\vartheta = \frac{t\ (or\ 1\ day\ in\ the\ Woodrow\ case)}{\ln\left[\dfrac{initial\ residue}{initial\ residue - (24 \times flux_{24-hr})}\right]} = \frac{1}{\ln\left[\dfrac{0.22}{0.22 - (24 \times 0.0032)}\right]} = 2.33 \text{ days} \qquad \text{Eqn. C3}$$

The average exposure within any chosen interval of duration from application to time *t* can be calculated by using this half-life within Equation C4.

$$\text{average over span "}t\text{"} = \text{initial flux H} \frac{\int_0^t \exp(-t/\tau)\, dt}{t} = \text{initial flux H} \frac{\tau \times (1 - \exp(-t/\tau))}{t} \qquad \text{Eqn. C4}$$

The first part of Table C1 presents a range of examples of these averages as a fraction of the initial value. The second part of Table C1 presents the ratios of the average within the designated interval to the average within the first 24-hours. The Panel commented that in the context of other short-term toxicological effects, it is notable that the maximum ratio between the first hour and the full 24-hours never exceeds 2-fold, at least within the range of half-lives examined. (Note: For this example, these values are smaller than the values given at the meeting.) Table C2 presents the instantaneous flux rates at the same points in time just for information. Again, the Panel pointed out that these extrapolations should be viewed only as a potential extension of the Woodrow model (a Tier IIA model) and should not be viewed as a replacement for estimations of flux rates from the more comprehensive models in Tier IIB. For instance, exponential dissipation based only on evaporation would over-estimate vapor exposures if the pesticide also dissipated into the soil and decayed by other mechanisms.

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[3] Equation C2is a simplification of Equation 4 in the Agency's background document for flux from foliage based on the following generic logic:

$\ln(\text{flux}) = A + B \ln(C \times P_{vapor}) = A + B \ln(C) + \ln(P_{vapor}^{\ B})$

$\text{flux} = e^{A + B \ln(C) + \ln(Pvapor)} = e^{A + B \ln(C)} \times e^{B \ln(Pvapor)} = e^{A + \ln(C)} \times P_{vapor}^{\ B}$

Table C1. Results of using an exponential decay model to extrapolate from the average flux values in the first 24-hours to the average over various other time intervals of hours (or days), "t" in Equation 8C.

Average within the interval as a fraction of the instantaneous initial value.

			interval of the average in hours					(7-days)	(21-days)
		τ in hours	1	2	4	8	24	168	504
HL =	0.5	17.312	0.972	0.944	0.893	0.801	0.541	0.103	0.034
in days	1	34.625	0.986	0.972	0.944	0.893	0.721	0.204	0.069
	2	69.249	0.993	0.986	0.972	0.944	0.845	0.376	0.137
	3	103.874	0.995	0.990	0.981	0.962	0.893	0.496	0.204
	4	138.499	0.996	0.993	0.986	0.972	0.918	0.579	0.268
	5	173.123	0.997	0.994	0.989	0.977	0.934	0.640	0.325
	10	346.247	0.999	0.997	0.994	0.989	0.966	0.792	0.527
	20	692.494	0.999	0.999	0.997	0.994	0.983	0.888	0.710
	30	1038.740	1.000	0.999	0.998	0.996	0.989	0.923	0.792

Ratio of the average value within the interval to the 24-hour average.

			interval of the average in hours					(7-days)	(21-days)
		τ in hours	1	2	4	8	24	168	504
HL =	0.5	17.312	1.796	1.746	1.650	1.480	1.000	0.190	0.063
in days	1	34.625	1.366	1.347	1.309	1.238	1.000	0.283	0.095
	2	69.249	1.175	1.166	1.150	1.117	1.000	0.445	0.162
	3	103.874	1.115	1.109	1.099	1.078	1.000	0.555	0.229
	4	138.499	1.085	1.081	1.074	1.058	1.000	0.631	0.291
	5	173.123	1.068	1.065	1.059	1.047	1.000	0.685	0.348
	10	346.247	1.034	1.032	1.029	1.023	1.000	0.820	0.545
	20	692.494	1.017	1.016	1.014	1.012	1.000	0.903	0.723
	30	1038.740	1.011	1.011	1.010	1.008	1.000	0.934	0.801

Table C2. Results of using an exponential decay model to extrapolate from the average flux values in the first 24-hours to the instantaneous flux at various other time intervals of hours (or days).

Fractional value at the end of each time period

			interval in hours					(7-days)	(21-days)
		τ in hours	1	2	4	8	24	168	504
HL =	0.5	17.312	0.944	0.891	0.794	0.630	0.250	6.1E-05	2.27E-13
in days	1	34.625	0.972	0.944	0.891	0.794	0.500	0.008	4.77E-07
	2	69.249	0.986	0.972	0.944	0.891	0.707	0.088	0.001
	3	103.874	0.990	0.981	0.962	0.926	0.794	0.198	0.008
	4	138.499	0.993	0.986	0.972	0.944	0.841	0.297	0.026
	5	173.123	0.994	0.989	0.977	0.955	0.871	0.379	0.054
	10	346.247	0.997	0.994	0.989	0.977	0.933	0.616	0.233
	20	692.494	0.999	0.997	0.994	0.989	0.966	0.785	0.483
	30	1038.740	0.999	0.998	0.996	0.992	0.977	0.851	0.616

Ratio of the average value within the interval to the average 24-hour value.

			interval in hours					(7-days)	(21-days)
		τ in hours	1	2	4	8	24	168	504
HL =	0.5	17.31	3.78	3.56	3.17	2.52	1.00	0.000	9.09E-13
in days	1	34.62	1.94	1.89	1.78	1.59	1.00	0.016	9.54E-07
	2	69.25	1.39	1.37	1.33	1.26	1.00	0.13	0.00
	3	103.87	1.25	1.24	1.21	1.17	1.00	0.25	0.01
	4	138.50	1.18	1.17	1.16	1.12	1.00	0.35	0.03
	5	173.12	1.14	1.14	1.12	1.10	1.00	0.44	0.06
	10	346.25	1.07	1.07	1.06	1.05	1.00	0.66	0.25
	20	692.49	1.03	1.03	1.03	1.02	1.00	0.81	0.50
	30	1038.74	1.02	1.02	1.02	1.02	1.00	0.87	0.63

Discussion of Tier IIB Flux Models

A summary of a number of suggestions made by different Panel members regarding the use of flux models is provided below.

1. Several Panelists suggested that the Agency use the volatilization flux models to explore an array of crop and use patterns and to explore multi-field applications and multiple applications of a given pesticide within a field. One variation on this theme was the idea of using the models to develop "sentinel" worst-case scenarios. Because worst cases can vary, an array of exposure scenarios should be explored stratified by chemical, crop, and region. An assumption of a unit flux should be used with an appropriate air dispersion model, or models, and representative historical meteorological data to identify worst-case scenarios and predicted vapor concentrations in air. Predicted concentrations for substances with fluxes not equivalent to unity can be estimated by multiplying the unit flux predictions by a given substance's flux. In the absence of information on particular pesticide fluxes, a literature review of losses over say 24-hours (*e.g.,* Smit *et al.*, 1998) may permit the identification of a reasonable worst case assumption of the proportion volatized that can be used to estimate the flux over the same time period.

2. The Panel believed that the way the models were used in the Agency's case studies was inappropriate. For example, PERFUM is a model that was developed and field validated to estimate fumigant volatilization and downwind movement and concentrations under typical fumigation field conditions, *i.e.*, flat, fallow fields, usually covered with plastic tarps. This model was not, as far as the panel members were aware of, validated for any other class of pesticide or other field conditions. Not only was this model used to evaluate semi-volatile pesticides with very different physicochemical properties than fumigants, it was also applied to field environments that were radically different (orchard and cabbage fields) from the typical fumigation field (fallow, flat). The only way this model, or any other for that matter, can be reliably used to predict source volatilization flux and downwind air concentrations is to field validate them under the typical field conditions the various pesticides in question will be used.

3. The confidence in using the PERFUM model for semi-volatile pesticides can be increased considerably by conducting several field volatilization/model evaluation studies on select semi-volatile pesticides used on a range of crop types (*e.g.*, cover crop, short row crop, tall row crop, orchard) in representative geographic and climactic areas (or major agricultural areas) where the selected semi-volatile pesticides will normally be used. The field and modeling data from these studies can then be further evaluated by applying/using the results from one study to each of those areas where the other studies were conducted, as was done in the presented case study. Then those results can be compared to the actual field and modeled results. This will show almost immediately if this kind of exercise has any validity. If the results show promise, then the models can be further refined/fine-tuned, and subsequent predictions of the model on other semi-volatile pesticides in other field situations can be better defended because the model has been rigorously tested and compared against a variety of actual field situations.

4. Another suggestion was to prioritize risks by starting with an acceptable concentration. This suggestion was independent of prioritizing based on use of the Vapor Hazard Ratio (VHR) discussed below.

5. Several panelists reiterated an earlier point made in response to Topic A to not decouple the flux and dispersion models.[4] Decoupling probably increased the variability in the outcome of the examples presented in the Agency background document because of the covariance between the effects of many of the same variables that affect both outcomes.

C.2) Does the Panel agree that the postapplication bystander inhalation risk estimate case study appropriately matches the duration of the exposure with the proper toxicological study of the same duration?

The Panel agreed that the case study appropriately matched the duration of the exposure with the proper toxicological end point, although there were some questions regarding the specificity of the target population within this particular case study. Again, a great deal of the Panel's discussion on Topic B apply here, particularly the limitations of the route-to-route extrapolation process and the need to apply toxicological data collected from one duration of exposure to another. Thus, the success of this case study to achieve its goal is tempered by the limited confidence that the Panel has in extrapolating toxicological data considering both route and duration of the exposure.

However, in a broader sense, the Panel agreed that the example did not adequately consider the ability to model differences in duration of the exposure. In earlier sections, the Agency presented three types of exposure scenarios for risk assessment, short- (up to 30 days), intermediate- (up to 90 days) and long-term (greater than 1 year). The example only presented modeled air concentrations for short-term exposures. The models did not estimate intermediate- and long-term exposures. Two of the five pesticides listed in Table 3 (of the Agency's background document) used for modeling short-term exposures have reported soil half-lives of greater than 150 days, illustrating that intermediate exposures from single applications may occur. The Panel recommended the Agency consider adding longer-term exposures of more than 30 days in the models to address intermediate and long-term chronic exposures and to match toxicological studies. People who live in agricultural communities for their entire lives may be exposed to volatilized pesticides that may pose chronic, life-long health risks.

The Panel had a number of points regarding the uncertainty of matching the duration of the exposure with the proper toxicological study of the same duration. A brief summary of these remarks is presented below. Most of these points were made previously during the Panel's response to charge questions in Topic B.

1. Several Panelists discussed uncertainty in the specifics of the exposed population used

[4] By using the term, "decoupling," the Panel was referring to running a Monte Carlo simulation on a range of weather conditions to determine an array of flux values via PRZM or PEARL. Subsequently, a statistical percentile from that array is used as an input to PERFUM which is then used to run a separate, but statistically independent Monte Carlo simulation on the same range of weather conditions.

within the Agency's case study and the implications to the appropriateness of the UFs that were applied to address concerns about children's protection. The Panel indicated that the answer to the charge question depends both upon the UFs that were applied and the quality of the toxicological data such as the inclusion of developmental toxicity studies or studies conducted during critical life stages (i.e., children, teenage years) in the database. A new suggestion that may have broad applicability to the Agency was to view developmental/reproductive oral studies as informative in terms of effects, but not to be used quantitatively in terms of inhalation toxicity. In oral studies, if developmental, reproductive, or childhood effects occur at significantly higher concentrations than the critical effect, this would provide qualitative information on whether these effects may occur at low concentrations after inhalation exposure.

Toxicology for Risk Assessment (TERA) organized three peer consultations, two in 2005 and one in 2007, on issues related to risk assessment for children. One of the 2005 consultations, together with the follow-up in 2007, addressed issues related to toxicokinetic differences between adults and children, and the second 2005 consultation addressed issues related to the adequacy of the database uncertainty factor: These documents are available at http://www.tera.org/peer/AdultChildTK/ACTKWelcome.htm.

2. The Panel reiterated that all of the previous discussion in Topic B regarding the applicability of Haber's law applies to this case study. In the end, without other inhalation study data, the Panel thought it was difficult to tell for most pesticides whether a toxicity study conducted at one duration of exposure extrapolated to another is appropriate as previously discussed.

3. Similarly, the Panel reiterated its discussion in Topic B regarding the limitations of route-to-route extrapolation.

4. One Panelist strongly suggested that the term "RfC" not be used to describe "reference concentration" if an oral toxicity study is used in a route-to-route extrapolation of inhalation toxicity. The term reference concentration is typically used for values where UFs have been applied to the appropriate point-of-departure; therefore, it would be inappropriate to use this term to describe a value that has not been adjusted for uncertainties in the data.

5. Another Panelist commented that the Agency should consider the advantages of setting a fixed value for the Margin of Exposure (MOE) before completing the exposure assessment versus evaluating the quality of the MOE that results from such an assessment.

6. In the context of future assessments of inhalation hazards, the Panel was interested in how the MOE approach could be used to combine the three routes of exposure via volatilization, spray drift, and respirable particles to assess cumulative or aggregate inhalation risk. Alternatively, the Panel suggested that it might be easier to calculate a Concentration of Concern (CoC) (which incorporates UFs) first and then calculate the hazard quotient (HQ), which is the ratio of the breathing level IE to the CoC. Hazard

quotients from different pathways (or from different pesticides) could be added together to calculate an overall hazard index (HI). For additional information, HQs from different pathways (or from different pesticides) could then be added to calculate a HI. If the resulting HQ or HI is ≤ 1, then adverse health effects would not be expected. If the HQ or HI is slightly > 1, then it would not necessarily mean that health effects would occur but that further evaluation was necessary. And if the HQ or HI is substantially > 1, then it would indicate health effects would be likely to occur. The hazard quotient would seem to offer a better alternative than a Margin of Exposure (MOE) approach to aggregate risk.

C.3) Please comment on the scientific strengths and weaknesses of conclusions and characterization regarding the estimated risks presented in the case study.

The Panel broadly agreed that the case study included all or most of the important elements to conduct a proper risk assessment. The strength of the inhalation toxicity and exposure data bases for the chemical chosen led the Panel to conclude that the inhalation hazard and exposures assessments, and MOE analysis were realistic based on field monitoring data. However, the Panel had a range of recommendations for how this model and the risk assessment process could be improved, and reservations, if such an analysis were applied to many other chemicals. For instance, the toxic endpoints are unlikely to be as strong for other chemicals, the details and general applicability of some steps in the process were not well-defined, PRZM or PEARL were not optimized for their application to the evaporation of semi-volatile pesticides, and the impact of the propagation of uncertainty and safety factors within the process on the final result is uncertain. An alternative risk assessment approach based on the VHR is presented below.

Strengths

The ability to predict the concentration of vapors emanating from pesticides sprayed onto fields and crops and to assess the risks to bystanders is challenging. The multi-component and multi-step models that predict exposure are not simple, and the toxicity data pertinent to these exposure patterns are rarely available. Given these challenges, the Panel was in broad agreement that the process being pursued by the Agency includes all the ingredients needed to characterize the risks of such vapor exposures. The Panel noted that the Agency did a credible job in the case study as presented. The Tier IIB flux models have the ability to integrate the variability in real world settings and to generate a distribution of exposures that can be useful in risk assessment. The magnitude of the variations in the results that were presented was internally consistent and seemed realistic. Also, the magnitude and distribution of the resulting MOEs were believable.

Weaknesses

In the larger sense, the Panel concluded that the case study is about as good of a result as this approach can achieve at the present time. The pesticide selected for this case study may be one of the few that have sufficient data to link exposures over different intervals with relevant toxicological data points. The Panel was not confident that this process could be extended to many other compounds because of the scarcity of data. The Panel concluded that filling the gap in vapor inhalation toxicity data and performing more field studies to validate the vapor flux and

dispersion models are at least equally important. However, filling the gap in data of vapor inhalation toxicity data would be more complex, take longer, and be more costly than conducting more field assessments (or utilizing more existing field studies) to increase confidence in the exposure values.

Several Panelists agreed that exposures as short as (or shorter than) 1 hour should be of interest to the Agency. As discussed in Topic A, such initial peak exposures should be derived either from a dynamic model or (preferably) from actual measurements over shorter intervals than has been the historic practice, and not from average conditions over longer intervals. However, it may turn out that exposures in the first hour are only about a factor of two greater than the averages in the first 24-hours (see Table C1, exposures predicted from an exponential decay model using Equation C4 above).

The Panel stated that the Agency should be more diligent in describing the uncertainty that surrounds each variable within the PRZM and PEARL models. The Panel provided several ways to better understand the uncertainties in each variable and suggested opportunities to increase the confidence in the model outcomes. For instance, the Panel identified multiple sources of uncertainty in both the predicted vapor exposures and in the exposure limits in the PRZM and PEARL models. Several panelists suggested that sensitivity analyses should be conducted on the variables within the models to distinguish the relative contributions of each variable to the model outcomes. Others commented on the perhaps more urgent need to have additional field studies conducted in different cropping scenarios to increase the confidence in the exposure value predicted by these models.

One Panelist stated that the toxicity estimates have uncertainties. There are several ways to express this uncertainty:

- Include a discussion of the UFs used to calculate the CoC, including the database UF. The larger the value of the UFs, the larger the uncertainty. If the Agency uses a MOE approach, the value of the level of concern (i.e., the value of the MOEs) would express the uncertainty.
- If the dose-response data are amenable to benchmark dose modeling, the ratio between the benchmark concentration (BMC), the central estimate, and the 95% upper confidence limit of the BMC (BMCL) is a quantitative measure of uncertainty in the dose-response data. The larger the ratio, the larger the uncertainty.
- A probabilistic method using the distribution of the UFs to calculate a CoC could be used to derive a range of CoCs and quantify uncertainty.

In discussing potential pesticide studies that could be used as a model for exposure through inhalation affecting multiple systems, one panelist suggested paraquat. There have been multiple studies on the inhalation toxicity of paraquat (Dinis-Oliveira *et al.*, 2008; Haley, 1979) om addition to its neurotoxic effects (Haley, 1979; Liou *et al.*, 1997; Dinis-Oliveira, 2006) and its use in animal models to study Parkinson's disease (Betarbet, 2000; Gorrell, 1998; Thirachelvam, 2000). The principal limitation in paraquat's use as a model chemical for inhalation risk assessment is that it is a charged compound. However, paraquat has a reported VP of $1x10^{-7}$ mmHg, low but similar to the VP for a couple pesticides in Table 3 and 4 in the Agency's background document. Moreover, there is potential inhalation exposure to paraquat (a defoliant),

e.g., smoking leaves of treated plants. Paraquat residues may be re-volatilized when smoking a cigarette, *i.e.*, the VP substantially increases when heated to a cigarette's burn temperature, for example. The smoke carries the paraquat into the deep long where it can be extracted by lung fluid. Re-volatilized residues would be estimated using flux models, assuming that they are sophisticated enough to account for mixtures (paraquat, water, and anything else that may be co-applied to the crop). Thus, paraquat can provide a working toxicological pesticide model for multisystem negative health outcomes associated with an inhalation pathway.

Alternative Risk Assessment Approach

The broad charge to the Panel for Topic C combined aspects of the exposure prediction in Topic A and the toxicological assessments in Topic B. The Panel discussed an alternative risk assessment approach that is applicable to the Occupational Safety and Health Administration (OSHA) and allows both hazard and exposure assessments to be combined in a simple, yet potentially useful way. Using this approach, the vapor exposure hazard is first separated into its chemical-specific components via the VHR and its environmental components via the "Environmental Dilution Ratio" [EDR]. A determination of acceptable exposures involves the simultaneous use of both ratios as EDR/VHR. In principle, both VHR and EDR involve only physical and toxicological properties; in that sense, they are strictly science. The final question of whether one decides that an acceptable value of the EDR/VHR ratio representing a given use condition for a particular pesticide should be a value of only 1 or an MOE of 100 or another level of concern is a policy decision.

A brief summary of the alternative VHR/EDR approach applicable to OSHA is provided below, and a more detailed explanation is provided in Appendix D. For OSHA, the acceptability of an exposure is defined by a simple ratio of the chemical concentration to which employees are exposed [abbreviated herein by C] divided by that chemical's exposure limit [EL] where health effects would not be expected to occur. The EL is often an OSHA permissible exposure limit [PEL] or Threshold Limit Value [TLV®]. Such EL values do not have explicit uncertainty factors built into them.. To be acceptable in those other settings, the EL for a given chemical must simply be greater than its measured or predicted C, or the ratio in Equation C5 must be greater than one.

$$\frac{EL}{C} \; must\ be > 1 \qquad \text{Eqn. C5}$$

Predicting an acceptable setting using Equation C6 is complicated because both EL and C are affected by so many variables. An alternative way to define this same level of acceptability is by using the ratio of two other ratios as shown in Equation C7. Both the EDR and the VHR are related to C and EL, respectively.

$$\frac{EL}{C} = \frac{EDR}{VHR} \; must\ be > 1 \qquad \text{Eqn. C6}$$

The VHR is mathematically defined by Equation C7 as the amount of dilution a given chemical needs between the chemical's saturated vapor concentration right at the source and an acceptable vapor concentration or EL value defined by the chemical's toxicity. A list of VHR values for pesticides was extracted from a broader list of chemicals compiled by Popendorf (2006) is found in Appendix D. This list was rank ordered from the pesticide with the highest VHR to the lowest VHR. These VHR values are not directly applicable to those the Agency might use. In the case of the Agency and this charge, a pesticide's toxicity would be defined quantitatively based on the duration of the exposure, *i.e.*, acute, sub-chronic, and chronic. Thus, each pesticide is likely to have a different VHR for each exposure scenario (but potentially a similar rank-order in each such scenario's list). Such a rank ordered list of VHR values could easily identify those pesticides with the greatest (and those with a negligible) vapor hazard. In this sense, the VHR provides a more useful list than a list based on the current Tier I criteria of just a chemical's vapor pressure. VHR values could also be modified slightly by including some of the soil interaction terms from the Tier IIA Woodrow model into the numerator for those pesticides that might have a higher flux from soil than from foliage.

$$VHR = \frac{P_{vapor} \ \ in\ units\ \ of\ \ ppm\ \ or\ \ mg/m^3}{exposure\ \ limit\ \ in\ the\ same\ units} \qquad \text{Eqn. C7}$$

The EDR is mathematically defined by Equation C8 as the amount of dilution that a given environmental setting can or does create between the chemical's saturated vapor concentration right at the source and the vapor concentration at any defined location, *e.g.*, 10 meters downwind of a sprayed field. A separate list of EDR values could be generated for various application and location settings using a combination of flux and dispersion models as currently proposed by the Agency. This procedure is analogous to what several panelists referred to as "back-calculating exposure."

$$EDR = \frac{P_{vapor} \ \ in\ units\ \ as\ \ in\ the\ VHR}{P_{partial} \ \ in\ any\ \ defined\ \ location} \qquad \text{Eqn. C8}$$

The criterion implied by Equations C5 and C6 do not incorporate any Margin of Exposure (MOE).To relate the EDR and VHR approach to the MOE approach for an "acceptable exposure" to a pesticide, the ratio of both EL/C and EDR/VHR would also need to exceed the MOE for that chemical, as depicted in Equation C9. An MOE with a value of 100, for example, would provide an added level of assurance that exposures (or doses) to pesticide workers or to the public will not exceed limits set based on toxicological studies in a laboratory.

$$\frac{EL}{C} = \frac{EDR}{VHR} \ must\ be > MOE \qquad \text{Eqn. C9}$$

Looking at uses of volatile (or semi-volatile) pesticides in terms of EDR and VHR values provides a method to evaluate the environmental conditions separately from the various pesticides. For instance, the Panel thought that the Agency could explore the use conditions that result in low EDR values and thereby target high risk crops (*e.g.*, as a function of foliage density or height), weather (*e.g.*, as a function of atmospheric stability or temperature), or regions (*e.g.*,

as a function of soil conditions). Similarly, the Panel noted that the Agency could identify those pesticides that have a high VHR based on an array of temporal exposure scenarios with their appropriate toxicological end points.

The following discussion illustrates how both the EDR and VHR have direct applications to the case study presented to the Panel in Section 5 of EPA's background document. The EDR in the case study is the ratio of saturated air concentration (in Table 4, these values are 660 $\mu g/m^3$ for chemical C_1 and 16 $\mu g/m^3$ for chemical C_2, or 209 $\mu g/m^3$ when combined[5]) divided by the predicted air concentration (Table 9 contains both a Tier IIA prediction of 5.3 $\mu g/m^3$ and the corresponding "Max 24-hour Air Concentrations" Tier IIB predictions of 2 or 4 $\mu g/m^3$ by PRZM and PEARL, respectively). These values yield an EDR of 209/5.3 = 39 for Tier IIA or 105 and 52 for PRZM and PEARL, respectively. These predicted EDR values are all reassuringly similar to the mean and range of the minimum observed EDR values corresponding to the "Percent Departures from Study" in Table 4.[6] An extension of this approach would be to create a table of VHR values structured like Table D-1 of Appendix D in which each exposure limit applicable to general industry is replaced by a HEC or RfC concentration applicable to pesticides. Assuming for the moment that the values in Table D-1 were applicable, then those pesticides with a VHR greater than EDR/MOE = 39/100 = 0.39, if used under the same conditions (*i.e.*, with the same EDR value), would result in an MOE of less than 100, an exposure level that is generally considered to be of concern.

EDITORIAL COMMENTS ON THE BACKGROUND DOCUMENT

Several panelists made the following editorial comments to improve the clarity and adequacy of the overall presentation of the issues in the Agency's background document.

Errors were noted in the Agency's Equations 2, 3, and 4, and Tables 4 and 5

The units in Equations 2, 3, and 5 should be given as $\mu g/m^2/hr$ (as in Woodrow *et al.*, 2001), not $g/m^2/hr$ as shown in the Agency's background document. This error was apparently not internal to the $\mu g/m^2/s$ flux predictions presented in Table 5; however, this discrepancy was disconcerting to the external reader trying to reconcile high gram values predicted by Tier IIA model as shown with models that predict evaporation of liquid solvents.

In Table 4, the ratio for Chemical B of the Tier I Model concentration of 340,000 ng/m^3 to the maximum monitored concentration of 27,700 ng/m^3 is 12.5 not 125 as implied by 12,493%. Another discrepancy that may or may not be due to an error was uncovered when trying to validate the Tier IIA flux rates for chemical D in Table 5. The only way to get the value of 0.91 $\mu g/m^2/s$ is to assume a depth into the soil at which the chemical was applied but which was

[5] The saturation vapor concentration of chemical C is based on its description of a 30:70 mixture (assumed to be a molar ratio) of isomer C_1 and isomer C_2 (p. 35 and 54) and Raoult's law such that the mixture's concentration is (660 x 0.3) + (16 x 0.7) = 209 $\mu g/m^3$. . Raoult's law is likely to apply to a neat mixture of these two chemicals because they are very similar to each other; however, both may behave non-ideally if they are diluted in water.

[6] The "Percent Departures from Study" values in Table 4 equal 100 x ([the Tier I Model Concentration] / [the Maximum Monitored Concentration] - 1) = 100 x (EDR - 1). . Similarly, the EDR = (% Departure/100) + 1. . The fact that the latter values in the table are "maximum" concentrations, mean that the resulting ratios and EDR values are the minimum values that have been observed.

not provided to the reader.

Table 8 and Table 10 Values

One Panelist made a minor editorial comment regarding certain toxicological calculations used in the case study. Some values in Table 10 do not correspond to corresponding values in Table 8. The same Panelist attempted to reproduce the HEC values in Table 8, but there was not enough information provided in the case study to do so. For clarity, the EPA should include the detailed equations and intermediate calculations used to calculate the Short Term (1-30 days), Acute HEC, and Short-term HEC from the 7-day and 21-day inhalation study.

Definition of Terms

One Panel member suggested that EPA define the meaning of different terms used in the background document, *e.g.*, concentration of concern (CoC); level of concern (LOC); acute, short-term, intermediate durations of the exposure. One concern was use of the abbreviation "IE" to describe the inhalation exposure to which an individual is exposed because of the potential confusion with the abbreviation of IEC. Perhaps, "ground-level concentration (GLC)" or "ground-level exposure concentration (GLEC)" would be a better term.

Latest Developments in Toxicity Assessments

The Agency should include references to the most up-to-date scientific methods in toxicity assessments for chemicals with adequate toxicity data and indicate they plan to use these techniques. There is no mention of the latest developments in toxicity assessments such as the use of benchmark dose modeling to calculate an appropriate point of departure, the use of categorical regression, the use of data to justify UFs that are different from the default UF of 10, the use of data to calculate chemical-specific adjustment factors, or the use of the Multiple Pass Particle Dosimetry Model (MPPD). The background document does not discuss the potential for certain segments of the population to have differential susceptibility, e.g., children compared with adults.

Physicochemical Properties

Information on physicochemical properties of the pesticides should be provided in the background document. Vapor pressure as well as solubility data would be helpful.

Haber's Rule

The Agency should provide a more thorough discussion of Haber's rule as modified by ten Berge et al. (1986) in the background document, *e.g.*, Jarabek (1995).

LOC for Pesticide C

In the case study, the LOC for Pesticide C was a factor of 30. A discussion on why a database UF was not considered would be helpful for transparency.

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Appendix A. Comparison of Measured Air Concentrations in Field Studies in the United Kingdom with Predicted Air Concentrations using EPA's Tier I Approach

The EPA background document "Scientific Issues Associated with Field Volatilization of Conventional Pesticides" included cases studies where field data showed lower measured concentrations than the proposed Tier I procedure estimated, see Table A-1 below. For these examples, the use of the proposed Tier I saturated air concentrations overestimate the observed concentrations by several orders of magnitude.

Table A-1. Tier I Saturated air concentrations (Cs) presented in EPA's document, "Scientific Issues Associated with Field Volatilization of Conventional Pesticides" (information taken from Tables 3 & 4)

Chemical	A	B	C1	C2	D
VP (torr)	9.70E-06	1.80E-05	3.00E-06	7.20E-07	2.40E-02
MW (g/mole)	263.21	350.59	406.92	406.92	189.32
Cs ($\mu g/m^3$)	137	340	66	16	244521
Maximum measured concentration ($\mu g/m^3$)	4.38	27.7	3.8	0.2	8.9
ratio of Cs to "maximum measured C"	31	12	174	80	27,474

The Chemicals Regulation Directorate in the UK commissioned several recent studies to monitor residues in air following applications of pesticides with a range of vapor pressures, the lowest of which are less than the case studies examples referred to in the EPA background document. These pesticides are shown in Table A-2. The Tier I saturated air concentration of trifluralin is estimated at about 1900 $\mu g/m^3$. In field experiments, however, the highest concentration observed was about 90 $\mu g/m^3$, see Figure A-1. This level of overestimation is similar to that observed in the case studies provided in the EPA background document.

Table A-2. Examples of Tier I Saturated air concentrations (Cs) for pesticides included in recent field studies performed in the UK for the Chemicals Regulation Directorate

Chemical	Trifluralin	Fenpropidin	Epoxiconazole	Tebuconazole	Prothioconazole
VP (Pa)	1.40E-02	1.70E-02	1.00E-05	1.30E-06	4.00E-07
VP (Torr)	1.05E-04	1.28E-04	7.50E-08	9.75E-09	3.00E-09
MW (g/mole)	335.5	273.5	329.76	307.81	312.2
Cs ($\mu g/m^3$)	1896	1877	1.33	0.162	0.0504

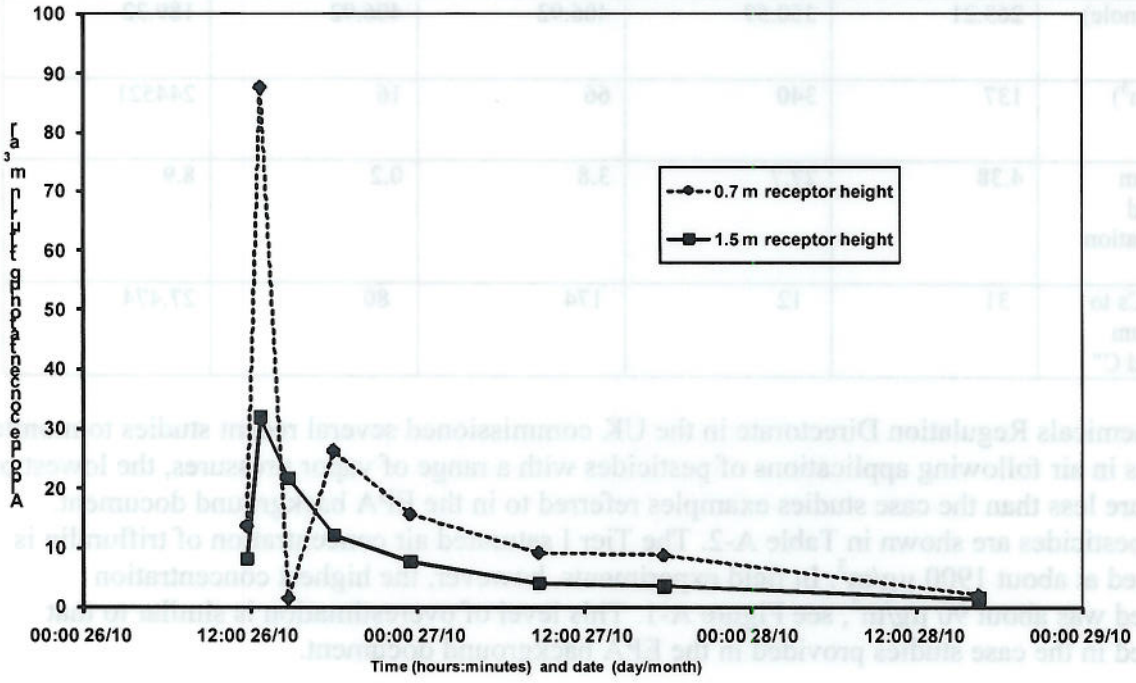

Figure A-1. Highest measured air concentrations during monitoring of trifluralin residues in air at receptor heights of 0.7 meters and 1.5 meters, both at 2 meters from the edge of 1 ha plot after application to bare soil without incorporation. [Data from 2007 Defra Project Report PS2008: Measurements of bystander contamination during and post the application of pesticides relevant to arable crops in typical UK conditions Part 2: studies with a volatile formulation, available online at: http://randd.defra.gov.uk/Document.aspx?Document=PS2008_5212_FRP.docm.

The Tier I saturated air concentration of fenpropidin is also about 1900 $\mu g/m^3$ while that of epoxiconazole is about 1 $\mu g/m^3$. These two pesticides were applied together as a tank mix of formulated products in a series of experimental trials. The results from the first trial are shown in Figure A-2 and Figure A-3. The observed concentrations of fenpropridin were usually higher than those of epoxiconazole, and at most were about two orders of magnitude below the Tier I estimate. However, on the first day, after the application was completed and on the next day concentrations of epoxiconazole were equivalent to the Tier I estimate were observed. In a second trial done in a later year, field concentrations of epoxiconazole were above the Tier I concentration (see Figure A-4).

The air sampling method for these pesticides involved the use of Occupational Safety and Health Administration (OSHA) versatile sampling (OVS) tubes. The first stage of these tubes is a filter that collects particles, and between a third and a half of the total pesticide in many air samples was found on the filter, but this mass is not included in the vapor phase concentration value. An absorbent to collect vapors comprises the second stage.

Members of the Panel questioned the possibility of a sampling artifact in the UK studies whereby particulate-phase pesticide residues were captured thereby increasing the measured air concentration value. The sampling artifact could have occurred if a portion of the particulate-phase pesticide was stripped from the filter during sampling and retained by the sorbent bed in the second stage of the sampler. If this mechanism were applicable, then much of the sample may not have been vapors in the field, and the vapor concentration may not have exceeded saturation. However, researchers in the UK had already anticipated this potential [artifact] and had undertaken a trial involving particulate sampling of epoxiconazole and fenpropidin using a personal cascade impactor collecting particles 0.3-50 μm alongside the OVS tubes. The results of this parallel sampling indicated no evidence that a significant proportion of the material collected in the OVS tubes was associated with contaminated particles. Further tests in a wind tunnel and observations of the dust collected confirmed that had significant quantities of contaminated particles been present in the air they would have been detected on the impactor plates (Defra Project PS2016).

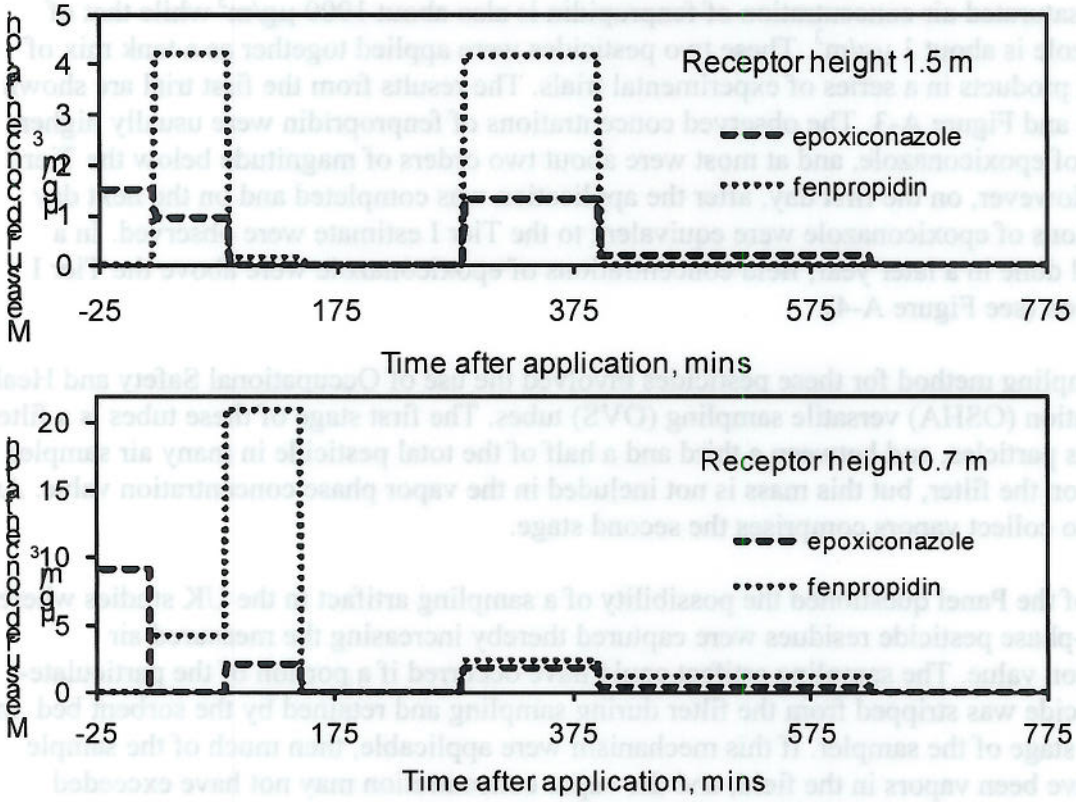

Figure A-2. Measured air concentrations of epoxiconazole and fenpropidin residues at two receptor heights, at 2 meters downwind from the edge of a 4.8 ha treated area following application to an established cereal crop in 2006. [Data from Defra Project PS2005, reported in Bulter-Ellis MC and Miller PCH (2008), Progress in the development of a bystander and resident exposure assessment model, Aspects of Applied Biology 84, 2008, International Advances in Pesticide Application.]

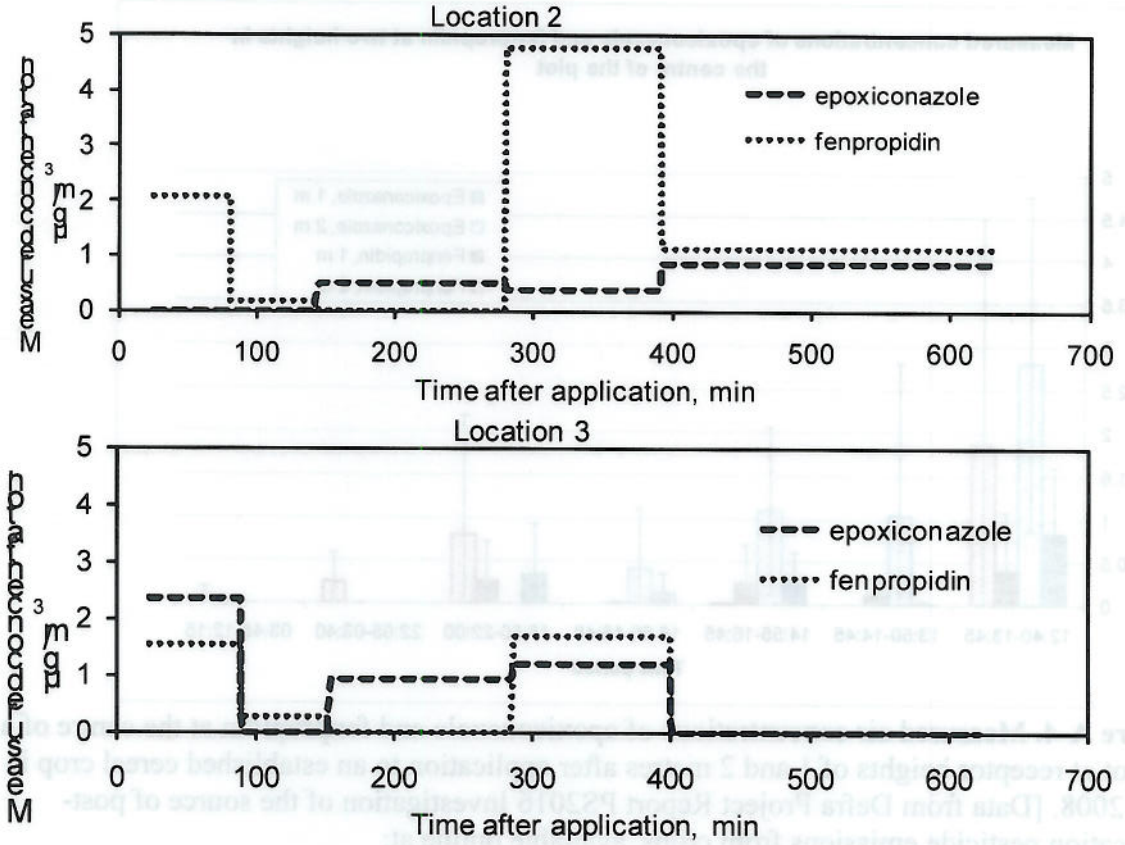

Figure A-3. Further results from monitoring of epoxiconazole and fenpropidin residues in air at 0.7 metre receptor height, at two additional locations both 2 meters downwind from the same application as referred to in Figure A-2 [Data from Defra Project PS2005, reported in Bulter-Ellis MC and Miller PCH, 2008, Progress in the development of a bystander and resident exposure assessment model, Aspects of Applied Biology 84, 2008, International Advances in Pesticide Application.]

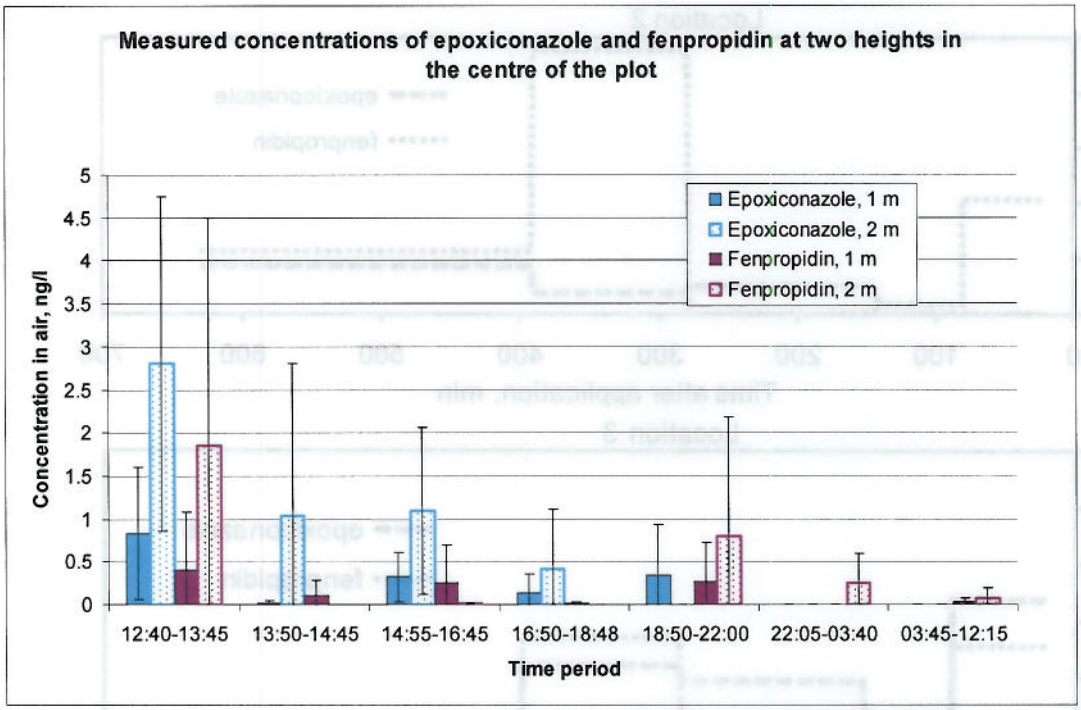

Figure A-4. Measured air concentrations of epoxiconazole and fenpropidin at the centre of a 3.7 ha plot at receptor heights of 1 and 2 metres after application to an established cereal crop in June 2008. [Data from Defra Project Report PS2016 Investigation of the source of post-application pesticide emissions from crops, available online at: http://randd.defra.gov.uk/Document.aspx?Document=PS2016_8607_FRP.doc.

The air sampling method for epoxiconazole, fenpropidin, thiabendazole and prothioconazole all involved the use of Occupational Safety and Health Administration (OSHA) versatile sampling (OVS) tubes. The first stage of these tubes is a filter that collects particles, and between a third and a half of the total pesticide in many air samples was found on the filter. An absorbent to collect vapors comprises the second stage. Whether a significant portion of the measured vapor could have been stripped from the particulate form on the filter and retained by the sorbent bed in the second stage was of some concern because if this mechanism were applicable, then much of the sample may not have been vapors in the field, and the vapor concentration may not have exceeded saturation. However, to investigate this possibility a trial with epoxiconazole, and fenpropadin, involving particulate sampling was done using a personal cascade impactor collecting particles 0.3-50 μm alongside the OVS tubes. The results of this parallel sampling indicated no evidence that a significant proportion of the material collected in the OVS tubes was associated with contaminated particles. Further tests in a wind tunnel and observations of the dust collected confirmed that had significant quantities of contaminated particles been present in the air they would have been detected on the impactor plates (Defra Project PS2016).

A third U.K. trial (Defra Project PS2023) was conducted in October 2009 at a laboratory independent of the first facility. In that trial a similar tank mix of epoxiconazole and fenpropidin were applied to grass. Preliminary results show that maximum concentrations of fenpropidin were similar to those in the previous trials, while maximum concentrations of epoxiconazole were slightly lowers those seen before.

Table A-3. Measured air concentrations of epoxiconazole and fenpropidin (mean of 3 samples) in the centre of a 12 meter untreated square in a large field following experimental application to a grass crop in 2009. [Preliminary data from Defra Project PS2023.]

	Epoxiconazole			**Fenpropidin**		
	OVS Sorbent ng m-3	OVS Filter ng m-3	Total ng m-3	OVS Sorbent ng m-3	OVS Filter ng m-3	Total ng m-3
30 min	66	410	476	6430	16047	22477
1 hour	<LOQ	<LOQ	<LOQ	7265	10414	17679
2 hours	<LOQ	<LOQ	<LOQ	4213	3538	7751
4 hours	<LOQ	<LOQ	<LOQ	2115	1963	4078
6 hours	<LOQ	<LOQ	<LOQ	87	604	691
8 hours	<LOQ	<LOQ	<LOQ	121	462	583
12 hours	<LOQ	<LOQ	<LOQ	85	509	594
24 hours	<LOQ	<LOQ	<LOQ	23	167	190
36 hours	<LOQ	1	1	10	136	146
48 hours	<LOQ	14	14	5	22	27
3 days	<LOQ	8	8	1	16	17

Finally, preliminary results are also available from monitoring a commercial application of products containing prothioconazole and tebuconazole to wheat in the summer of 2009, the Tier I estimates for these compounds are 0.05 and 0.2 $\mu g/m^3$, respectively. These data, Table A-4, show that the maximum air concentrations of tebuconazole were about $1/10^{th}$ of the Tier I estimate. However, the maximum observations for prothioconazole were above the Tier I estimate for that compound. These observations cast doubt on the reliability of the proposed Tier I approach particularly for compounds with low vapor pressures.

Table A-4. Measured air concentrations of prothioconazole and tebuconazole (mean of 3 samples) in the centre of a 12 meters untreated square in the centre of a large field following a commercial application to a cereal crop in 2009. [Preliminary data from Defra Project PS2023.]

	Prothioconazole			**Tebuconazole**		
	OVS Sorbent ng m-3	OVS Filter ng m-3	Total ng m-3	OVS Sorbent ng m-3	OVS Filter ng m-3	Total ng m-3
15 min	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
1 hour	7.78	<LOQ	7.78	<LOQ	<LOQ	<LOQ
2 hours	38.33	21.11	59.44	<LOQ	16.39	16.39
4 hours	44.17	35.14	79.31	<LOQ	16.53	16.53
6 hours	38.06	22.36	60.42	<LOQ	4.44	4.44
8 hours	59.17	57.92	117.09	<LOQ	5.42	5.42
12 hours	48.33	32.01	80.34	<LOQ	5.35	5.35
24 hours	24.68	4.17	28.85	0.93	4.54	5.47
36 hours	43.33	29.1	72.43	1.78	2.45	4.23
48 hours	23.08	1.76	24.84	3.26	15.05	18.31
3 days	3.78	1.26	5.04	<LOQ	0.79	0.79
4 days	2.73	1.33	4.06	<LOQ	0.91	0.91
5 days	1.44	0.66	2.1	<LOQ	0.37	0.37
6 days	0.88	0.39	1.27	<LOQ	0.49	0.49
7 days	0.84	<LOQ	0.84	0.22	<LOQ	0.22
8 days	0.24	<LOQ	0.24	<LOQ	<LOQ	<LOQ
9 days	0.22	<LOQ	0.22	<LOQ	<LOQ	<LOQ
10 days	0.2	<LOQ	0.2	<LOQ	<LOQ	<LOQ
11 days	0.19	<LOQ	0.19	<LOQ	<LOQ	<LOQ
12 days	<LOQ	<LOQ	<LOQ	0.08	<LOQ	0.08

Appendix B. Three Approaches for Predicting Vapor Pressure of a Chemical within a Mixture

Note: One panelist provided this discussion adapted from Chapter 6 of *Industrial Hygiene Control of Airborne Chemical Hazards* by W. Popendorf (CRC Press, 2006).

The vapor pressure of a chemical within a mixture can be predicted by three basic approaches:

- Raoult's Law for ideal mixtures,
- an empirical adjustment to Raoult's Law for non-ideal mixtures, and
- Henry's Law for dilute mixtures in water.

Each approach has its advantages. Raoult's Law is simple, but many mixtures are not ideal. Unfortunately, failure to anticipate that a mixture is not "ideal" usually results in underestimating the health hazard or/and overexposing people to mixtures evolving organic vapors. Empirical coefficients are illustrative of non-ideal effects but are not simple to predict. And Henry's Law coefficients exist for many chemicals in water, but their accuracy is limited to very dilute mixtures.

Raoult's Law for Ideal Liquid Mixtures

Raoult's law is based on the premise that molecules within a liquid mixture all act independently of each other, leading to the logic that the number or density of molecules of each component in the mixture that would be present at the liquid's surface at any given moment would be reduced in proportion to that component's molar fraction within the liquid. Raoult's Law can be written as Eqn. B-1.

$$P_{vapor,\,i} = X_i \times P_{vapor} \qquad \text{Eqn. B-1}$$

The notation $P_{vapor,i}$ is used to designate the i^{th} chemical's vapor pressure when it is present as a component of a liquid mixture. The symbol X_i, indicates each component's molar concentration in the liquid state, *viz.*, X_i is the moles of component "i" per mole of liquid mixture.

Chemical mixtures that obey Raoult's Law are called an ideal mixture, and mixtures that deviate from Raoult's Law are called non-ideal mixtures. Most chemicals behave like a component in an "ideal mixture" when it is present at high liquid concentrations (more than 50% pure) or/and when its molecules are structurally similar to the molecules of the other components within a mixture. Unfortunately, the molecular interactions within mixtures of organic solvents and water are sufficiently strong that such mixtures often deviate from Raoult's Law.

The Need for an Empirical Adjustment to Raoult's Law

The more different that the molecules in a liquid mixture are from each other, the more likely they are to interact and their vapor pressures are to deviate from Raoult's Law. The opportunity for different molecules to interact is small as long as there are still many identical molecules around (*i.e.*, when the mixture is relatively concentrated), but deviations will get larger when most of the other molecules are "different" (*i.e.*, when a component in a mixture is dilute).

An "activity coefficient" is used in chemical engineering to adjust Raoult's simple, logical law for ideal mixtures to match the behavior of non-ideal liquid mixtures. This activity coefficient is given the symbol "γ" (a lowercase Greek gamma). This γ is sometimes also referred to as a "fugacity coefficient." Equation B-2 both defines γ, mathematically, and expresses the empirical concept behind it.

$$\gamma_i = \frac{measured\ or\ actual\ P_{vapor,i} = Y_i \times P}{Raoult's\ P_{vapor,i} = X_i \times P_{vapor}} \qquad \text{Eqn. B-2}$$

In a mixture, each component "i" will have its own γ_i. Each component's activity coefficient could be used in Eqn. B-3 to predict the absolute vapor pressure in units such as mmHg. Equation 3 will revert to Raoult's law (Eqn. 1) when γ =1.

$$P_{vapor,i} = \gamma_i \times X_i \times P_{vapor} = \gamma_i \times \text{Raoult's predicted } P_{vapor,i} \qquad \text{Eqn. B-3}$$

Figure B-1 can provide some graphical insight into how values of six organic solutes in water vary both among the six chemicals and also within each mixture as a function of "X." This figure shows how values increase as each solution gets more dilute and as the molecules become more dissimiliar from water. The γ^{∞} for very symmetric organic molecules like benzene occurs off-scale. The smallest γ^{∞} in this figure is for methanol because it is the chemical most similar to water. A γ value greater than one means that the component's vapor pressure is greater than predicted by Raoult's Law. Most organic chemicals when diluted in water will present a surprisingly high vapor hazard if their activity coefficient is not anticipated.

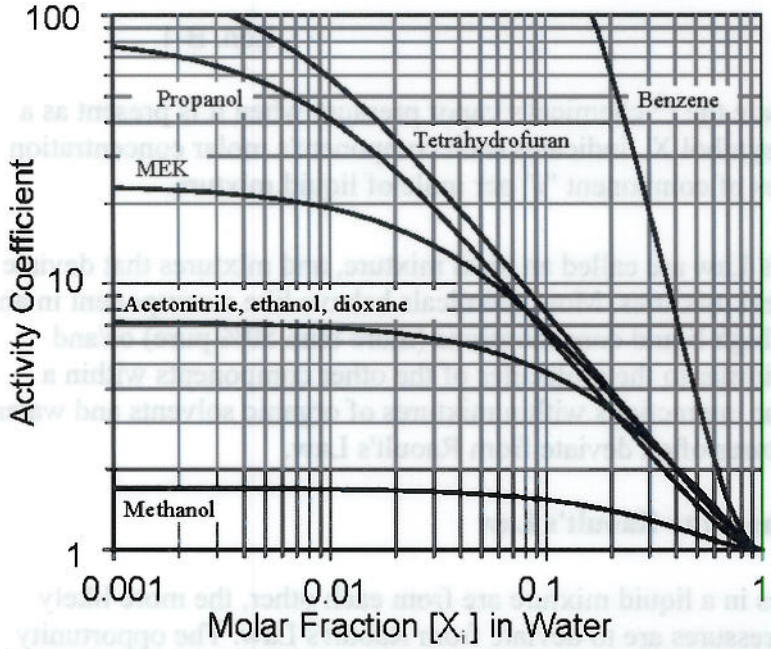

Figure B-1. Activity coefficient [γ_i] values for selected organic solutes in water. Adapted from Popendorf (2006).

Methods to Predict an Empirical Adjustment to Raoult's Law

The following four approaches to predict the activity coefficient γ_i were adapted primarily from Chapter 11 of the *Handbook of Chemical Property Estimation Methods* (Lyman et al., 1982), a jewel of a resource if one is challenged to estimate an otherwise hard-to-get or non-existent property value. Other sources of property estimation methods are also available (Reid *et al.*, 1987; Poling *et al.*, 2001). The middle two methods below rely on experimental data for the particular mixture, while the first and last methods can estimate γ without prior mixture-specific measurements.

A method first developed by Pierotti *et al.* (1959) and refined by Grain (1982) can be used to predict γ^∞ for binary mixtures. The method shown below in Eqn. 4 was described by Grain as "easy" in that its seven coefficients are based on the *overall* molecular structure of the solute and solvent (rather than on each component's individual moieties as in the Universal Functional Activity Coefficient (UNIFAC). Lyman's book contains four pages of tables and internal correction factors for the seven variables included in Eqn. 4.

$$\log \gamma_1^\infty = A_{1,2} + B_2 \times \left[\frac{N_1}{N_2}\right] + \left[\frac{C_1}{N_1}\right] + D \times (N_1 - N_2)^2 + \left[\frac{F_2}{N_2}\right] \qquad \text{Eqn. B-4}$$

The van Laar equation (*ca.* 1910) provides a generic relationship to estimate γ_i at any concentration based only on γ_1^∞ and γ_2^∞ derived either from measurements or other predictive methods (Hirata *et al.*, 1975; Poling *et al.*, 2001; Grain, 1982).

$$ln\,\gamma_1 = ln\,\gamma_1^\infty \times \left[1 + \frac{X_1\, ln\,\gamma_1^\infty}{X_2\, ln\,\gamma_2^\infty}\right]^{-2} \qquad \text{Eqn. B-5}$$

The most robust method to predict activity coefficients is via the group contribution method of UNIFAC (Poling *et al.*, 2001; Bishop *et al.*, 1982). While some software is available to implement the method, the lack of a database that defines the structures of even common chemicals or/and a user-friendly interface has kept these programs from being widely used.

Data in the Table B-1 excerpted from Grain (1982) allows one to compare activity coefficients at infinite dilution [γ^∞] for five common organic liquids in water The first column of γ^∞ values were experimentally measured; the second column of γ^∞ values were calculated by UNIFAC. The range of the percent errors by which the calculated γ^∞ differs from the measured γ^∞ that are presented in the third column of data suggests that UNIFAC does not always predict activity coefficients accurately. However, even the highest of these errors (131% for toluene in water) is much better than the 339,000% error that would result if no γ^∞ value were used at all (equivalent to assuming Raoult's Law or $\gamma^\infty = 1$ versus the γ^∞ of 3390 measured experimentally).

Table B-1. Comparison of activity coefficients at infinite dilution [γ^{∞}] for five common organic liquids in water (excerpted from Grain, 1982)

	Experimental γ_i^{∞} in water	Calculated γ_i^{∞} in water	% error	Experimental γ_{water}^{∞} in organic	$\frac{\gamma^{\infty}\ organic\ solvent}{\gamma^{\infty}\ water}$
Hexane	489,000	402,000	-18%	1880	260
Toluene	3390	7820	131%	3320	1.0
Benzene	1730	1670	-3.5%	226	7.7
Aniline	34.2	50.6	48%	4.98	6.9
Acetone	6.80	5.69	-16%	5.64	1.2
	average absolute error = 43%				

Henry's Law

Henry's Law assumes that the vapor pressure of component "i" [$P_{vapor,i}$] is proportionate to X_i via a fixed empirical coefficient called either a "Henry's Law constant" or "Henry's Law coefficient" denoted by the symbol "H_i" herein. A common expression of Henry's Law might look like Eqn. B-6.

$$P_{vapor,i} = H_i \times X_i \qquad \text{Eqn. B-6}$$

The major advantage of Henry's Law is the widespread availability of its constants (Lyman *et al.*, 1982; Yaws, 1992; MacKay *et al.*, 1992; Howard and Meylan, 1997; Sander, 2004). Unfortunately, the diverse origin of these coefficients has created an additional inconvenience because they have been developed with a considerable amount of variability in the units of H_i. Fortunately, on-line converters are available, *e.g.*, at the following sites:

www.mpch-mainz.mpg.de/~sander/res/henry-conv.html

www.epa.gov/athens/learn2model/part-two/onsite/henryslaw.htm

The limitation that Henry's Law only applies to dilute mixtures follows from the fact that H_i is a constant, independent of X_i. Based on the prior discussion of how γ_i decreases as the mixture gets less dilute, the relationship between H_i and γ_i can be found by equating a very dilute component's vapor pressure predicted by the empirical adjustment to Raoult's Law (Eqn. B-3) to that predicted by Henry's Law (Eqn. B-6).[7]

$$P_{vapor,i} = H_i\ X_i = \gamma_i\ X_i\ P_{vapor} \qquad \text{(repeating Eqns. B-3 and B-6)}$$

[7] While the relationship in Eqn. B-6 is conceptually true, technically γ^{∞} can only be unitless as shown, if both H_i and P_{vapor} have the same units. . Unfortunately, their units will likely not be the same, nor will their units be those commonly used within industrial hygiene.

$$H_i = \gamma^{\infty}_i P_{vapor}$$ Eqn. B-7a

$$\gamma^{\infty}_i = \frac{H_i}{P_{vapor}}$$ Eqn. B-7b

Henry's Law coefficient [H_i] will be constant as long as the component's concentration is sufficiently dilute that γ_i stays equal to the constant γ^{∞}. This range is best seen in Figure B-1. The curves of most activity coefficients flatten out to a constant γ^{∞} by the time the liquid molar concentration decreases to about 10^{-3}. The γ^{∞} of a few chemicals with small γ^{∞} values is already constant by the time the X_i reaches 10^{-2}, while those with large γ^{∞} values aren't constant until X_i is less than 10^{-4}. But in all cases, continued use of a Henry's constant for more concentrated mixtures will eventually over-estimate the real component's vapor pressure and its resulting airborne exposures.

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Appendix C. Alternative Approaches to Assess Inhalation Hazard in the Absence of Inhalation Toxicity Studies

One Panelist provided a discussion of alternative analytical approaches to assess inhalation hazard in the absence of inhalation toxicity studies. These approaches are screening approaches and do not involve a chemical-specific hazard identification and dose-response analyses. These screening approaches are Threshold of Regulation, Threshold on No Toxicological Concern, and the NOAEL-to-LC_{50} approach. These approaches were originally developed to evaluate oral exposure to trace levels of chemicals and to determine if toxicity testing should be required for those chemicals. There are only a few studies that evaluate inhalation hazard in the absence of inhalation toxicity studies and the exposure durations in these studies [chronic, lifetime exposure (Drew and Frangos, 2007) and one-hour intermittent exposure (Grant *et al.*, 1997)] do not correspond to the exposure durations the Agency is evaluating. Therefore, the majority of the Panel does not endorse the Drew and Frangos (2007) or Grant *et al.* (2007) approaches be used for pesticides in the interim in lieu of new inhalation toxicity studies. The following material is provided for informational and completeness purposes.

A Tiered Approach to Evaluate Acute Inhalation Toxicity (Texas Commission on Environmental Quality)

During the air permit review process, the Toxicology Division (TD) of the Texas Commission on Environmental Quality (TCEQ) frequently evaluates chemicals with limited toxicity data (LTD). When the minimum acute database requirement (as discussed in Section 3.4 of the Effects Screening Level (ESL) Guidelines (TCEQ, 2006)) is not met, an acute inhalation reference value (ReV) protective of a 1-hr intermittent exposure, is not developed. Instead, a tiered approach is used to either set a default screening value (i.e. Threshold of Regulation) or derive a generic health-based screening value depending on the availability of toxicity information and time and resource constraints (Figure C-1).

- Tier I – Threshold of Regulation (default ESL = 1 µg/m3)
- Tier II – Threshold of Concern and Use of LC_{50} Data (generic ESL)
- Tier III – Relative Toxicity/Potency Approach (generic ESL)

For the TCEQ, a generic short-term ESL is typically based on a one-hour averaging time. The following sections discuss the procedures used to set health-protective concentrations for LTD chemicals based on a tiered approach and the strengths and weaknesses of these approaches. The Tier III - Relative Toxicity/Potency Approach will not be discussed.

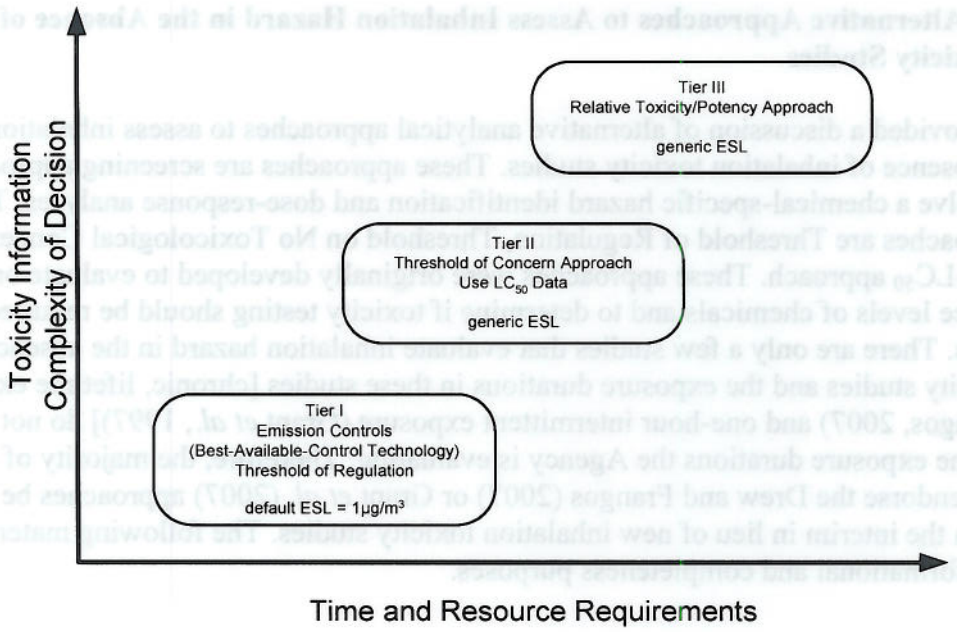

Figure C-1. A three-tiered approach to setting a default or a generic health-based ESL.

A Threshold of Regulation Approach

A Threshold of Regulation (TR) approach seeks to answer the question "if the concentration of a chemical in air is small, how small does an exposure have to be before it can defensibly be regarded as presenting trivial risk". Other terms used to describe this approach are "threshold of concern" or "threshold of no toxicological concern." Drew and Frangos (2007) provide a concise review of the statistical, analytical procedures used to establish the Threshold of Regulation approach adopted by US FDA and other organizations for oral exposure and its use in regulatory toxicology. Briefly, the fifth percentile of the cumulative percentage distribution of NOAELs in a large oral exposure database was determined and divided by an uncertainty factor of 100 (to account for animal-to-human uncertainty and human variability) to derive an estimate of an acceptable oral intake. Other investigators have used this approach for other products such as food flavorings, personal and household care products and pharmaceutical compounds (see Drew and Frangos (2007) and Grant *et al.* 2007 for references). Drew and Frangos (2007) developed a concentration of no toxicology concern (CoNTC) for evaluation of trace organic chemicals in air for evaluation of chronic exposure. This conservative generic CoNTC was derived by performing a route-to-route extrapolation from the virtually safe oral dose of 1.5 µg/person/day divided by a factor of two. Drew and Frangos (2007) proposed a generic CoNTC of 0.03 $\mu g/m^3$. It does not apply to metals, particulates or chemicals that produce sensory irritation.

Historically, the TCEQ has used a default of 1 $\mu g/m^3$ as a TR value for evaluation of a 1-hr intermittent exposure compared to the value of 0.03 $\mu g/m^3$ developed by Drew and Frangos (2007) for evaluation of chronic exposure. A value of 1 $\mu g/m^3$ is conservative. Based on an acute inhalation database for 97 chemicals, the fifth percentile of NOAELs would be 560 $\mu g/m^3$ (see Table 3, Grant *et al.*, 2007), and with a UF of 100 applied, it would be 5.6 $\mu g/m^3$ as a TR value for evaluation of a 1-hr intermittent exposure. This TR concentration is an estimate of threshold

air concentrations below which no appreciable risk to the general population would be expected to occur after a one-hour intermittent exposure.

Strengths:

1. A TR approach is conservative since inhalation toxicity of the most toxic chemicals is used to predict toxicity for all chemicals.
2. When a TR approach is used, inhalation toxicity information for a pesticide is not required – only the monitored/modeled vapor concentration
3. The TR value is based on statistical analyses of inhalation toxicity data, and the variability in the TR value can be determined
4. There is precedent in using a TR approach in a regulatory setting for oral data (*e.g.*, FDA 1995).
5. The monitored/modeled vapor concentration of semi-volatile pesticides in air are present in trace concentrations, and may be below the TR value.
6. Unnecessary animal studies are not performed because it identifies those chemicals that need additional testing.

Weaknesses:

1. The TR approach is only as good as the inhalation database used to derive the values. To develop a TR approach to evaluate different durations of exposure, one would need an adequate inhalation database for each exposure period. At the present time, an adequate database of inhalation toxicity data for vapors of pesticides for the durations of exposure the Agency uses in its assessment are not available.
2. The TR approach is conservative, and only chemicals that are present in air in trace concentrations would be screened out.
3. Since it is more difficult to conduct inhalation toxicity studies, the numbers of acceptable inhalation toxicity studies for vapor-phase semi-volatile pesticides would be small compared to oral toxicity studies.
4. The TR approach is a screening approach and does not involve a chemical-specific hazard identification and dose response analyses. Therefore, it does not produce a reference value that can be used in a margin-of-exposure approach or cannot be used to calculate a hazard quotient. Therefore, this screening approach does not lend itself to a cumulative assessment of different pathways of exposure or pesticides.

Classification System to Categorize Chemicals into Different Toxicity Potency Classes

If a classification system can be derived to categorize chemicals into different inhalation toxicity potency classes, then a Tier II threshold of no toxicological concern can be derived for each toxicity potency class. Drew and Frangos (2007) provide a concise review of determining a threshold of toxicological concern for different potency classes using the Cramer classification system (Cramer, 1978) for oral toxicity studies.

For oral exposure, the Cramer classification system successfully assigns chemicals into separate toxicity potency classes. For inhalation toxicity, both Grant *et al.* (2007) and Ford *et al.* (2006)

determined that the Cramer classification system (*i.e.*, a structurally –based system based on oral exposure) does not adequately place chemicals in separate toxicity potency classes predictive of inhalation exposures, so a structural alert system is not available for inhalation toxicity. The main difficulty is the inability to accurately predict whether chemicals would cause respiratory tract point-of-entry effects: "Currently, there are no internationally recognized screening methods in animals to predict the ability of chemicals to cause local effects of the respiratory tract" (Rennen *et al.*, 2004).

Grant *et al.* (2007) used LC_{50} data to classify chemicals into different inhalation toxicity potency classes. Ninety-seven chemicals were classified based on the Globally Harmonized System of Classification and Labeling of Chemicals proposed by the United Nations into different acute inhalation toxicity categories (from most toxic to least toxic): Category 1, Category 2, Category 3, Category 4, and Category 5. The tenth percentile of the cumulative percentage distribution of NOAELs in each category was determined and divided by an uncertainty factor of 100 to derive the following health-protective threshold of concern (TOC) concentrations for inhalation exposure: 4 $\mu g/m^3$ for chemicals classified in Category 1, 20 $\mu g/m^3$ for Category 2, 125 $\mu g/m^3$ for both Categories 3 and 4, and 1000 $\mu g/m^3$ for Category 5. These TOC concentrations are estimates of threshold air concentrations below which no appreciable risk to the general population would be expected to occur after a one-hour intermittent exposure.

Strengths:

1. By having a classification system to divide chemicals into different inhalation toxicity classes, one single threshold of regulation based on the most toxic chemical in the entire dataset is not used for a relatively nontoxic chemical.
2. This approach is conservative since the most toxic chemical within each class is used to represent the inhalation toxicity of all chemicals within one class.
3. The TOC values for each potency class are based on a statistical analysis of inhalation toxicity data, and the variability in the TOC value can be determined.
4. There is precedent in using a TOC approach in a regulatory setting, mainly for oral data
5. Unnecessary animal studies are not performed because it identifies those chemicals that need additional testing.

Weaknesses:

1. This approach is only as good as the inhalation database used to derive the values. At the present time, an adequate database of inhalation toxicity data for vapors of pesticides for the durations of exposure the Agency uses in its assessment are not available.
2. A predictive structural classification system is not available for inhalation data, so LC_{50} data are required.
3. Since it is more difficult to conduct inhalation toxicity studies, the numbers of acceptable inhalation toxicity studies is small compared to oral toxicity studies, so the numbers of chemicals in each separate toxicity potency class is small. This increases the uncertainty in the inhalation TOC concentrations.

4. This approach of classifying chemicals into different potency categories requires more inhalation toxicity studies than a single TR approach discussed above or the LC_{50} to NOAEL Ratios approach discussed in the following section.
5. The TOC approach is a screening approach and does not involve a chemical-specific hazard identification and dose response analyses. Therefore, it does not produce a reference value that can be used in a margin-of-exposure approach or cannot be used to calculate a hazard quotient. Therefore, this screening approach does not lend itself to a cumulative assessment of different pathways of exposure or pesticides.

LC_{50} to NOAEL Ratios

Layton *et al.* (1987) used oral LD_{50} data for estimating acceptable daily intakes for the evaluation of exposures to contaminants at hazardous waste sites. Venman and Flaga (1985) also proposed the use of LD_{50} data to establish provisional acceptable daily intakes for the evaluation of waste water contaminants. Both investigators calculated the ratio of NOAELs from chronic animal studies to oral LD_{50} data for different chemicals and determined the fifth percentile of the cumulative distributions of the ratios. The LD_{50} value for contaminants with limited toxicity data was multiplied by the fifth percentile ratio to derive a surrogate NOAEL. The surrogate NOAEL was divided by an UF of 100 in order to establish a conservative threshold dose below which no appreciable risk to human health would be expected to occur. Grant *et al.* (2007) used the basic approach of Layton *et al.* (1987) and Venman and Flaga (1985) for evaluating chronic oral toxicity and applied it to acute inhalation toxicity. Therefore, ratios of NOAELs from acute inhalation studies to LC_{50} data were calculated.

For the NOAEL-to-LC_{50} ratio approach, 55 chemicals with an inhalation NOAEL for an exposure duration $\leq$ 24-hours were used to calculate NOAEL-to-LC_{50} ratios. The tenth percentile of the cumulative percentage distribution of the ratios was calculated and divided by an uncertainty factor of 100 to produce a composite factor equal to 8.3×10^{-5}. For a chemical with limited toxicity information, this composite factor is multiplied by a 4-hour LC_{50} value or other appropriate acute inhalation lethality data as defined in Grant *et al.* (2007) to produce an estimate of a conservative threshold air concentration below which no appreciable risk to the general population would be expected to occur after a one-hour intermittent exposure.

Strengths:

1. LC_{50} data are available for most chemicals.
2. LC_{50} data are predictive of acute inhalation toxicity, since LC_{50} data were able to categorize chemicals into statistically significant distributions and toxicity potency classes.
3. This approach is conservative since the 5^{th} or 10^{th} percentile NOAEL-to-LC_{50} ratio is applied to the chemical-specific LC_{50} data.
4. The NOAEL-to LC_{50} ratio approach is based on a statistical analysis of inhalation toxicity data, and the variability in the ratio can be determined.

Weaknesses:

1. This approach is only as good as the inhalation database used to derive the values. At the present time, an adequate database of inhalation toxicity data for vapors of pesticides for the durations of exposure the Agency uses in its assessment are not available.
2. There should be an acceptable number of LC_{50} data and matching inhalation NOAEL data for each duration of exposure being evaluated.
3. Since it is more difficult to conduct inhalation toxicity studies, the numbers of acceptable pesticide inhalation toxicity studies is small, so the number of NOAEL-to-LC_{50} ratios may be inadequate.
4. This approach is a screening approach and does not involve a chemical-specific hazard identification and dose response analyses. Therefore, it does not produce a reference value that can be used in a margin-of-exposure approach or cannot be used to calculate a hazard quotient. Therefore, this screening approach does not lend itself to a cumulative assessment of different pathways of exposure or pesticides.

Time Extrapolation Factors or Assessment Factors

Refer to Kalberlah *et al.* (2002), Kramer *et al.* (1995, 1996), and Malkiewicz *et al.* (2009) for a discussion of time extrapolation or assessment factors. These references are provided for informational and completeness purposes only.

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Appendix D. Derivation and Elaborations on the Concepts of "Vapor Hazard Ratio" [VHR] and the "Environmental Dilution Ratio" [EDR]

Note: The following discussion is based on Chapters 5 and 8 of *Industrial Hygiene Control of Airborne Chemical Hazards* by W. Popendorf (CRC Press, 2006) and W. Popendorf: Vapor Pressure and Solvent Vapor Hazards. Amer. Ind. Hyg. Assoc. J., 45(10): 719-726 (1984).

With the eventual goal in mind of providing a theoretical framework for separating factors intrinsic to the chemical from factors intrinsic to the environment, this discussion begins with an explanation of evaporation. Although vapor pressure is not the only factor that affects evaporation, it is the only factor that is intrinsic to the chemical. All of the other variables that affect the evaporation rate depend either upon the physical nature of the liquid source (like its size and shape) or upon the speed and turbulence of the passing air.

As the vapors are swept away from the liquid surface by the passing air, more molecules evaporate from the liquid to maintain that same very localized equilibrium. Thus conceptually, the rate of evaporation is determined by how fast vapor molecules can diffuse across a thin, low speed "*boundary layer*" of air that always exists very close to a liquid surface. The thickness of that boundary layer (typically only a few millimeters along the vertical axis in Figure D-1) is determined by the air velocity, its turbulence, and the geometry of the liquid source (or its container if applicable).

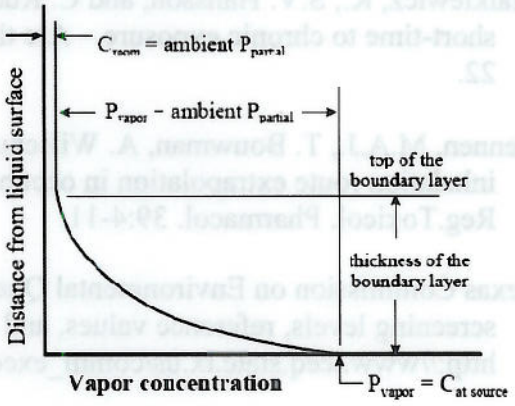

Figure D-1. Depiction of evaporation as diffusion due to a concentration difference across a boundary layer.

The vapor concentration (the horizontal axis in Figure D-1) at the liquid surface at the bottom of this boundary layer is always equal to the chemical's vapor pressure [P_{vapor}]. The concentration at the top of the boundary layer is the ambient concentration [ambient $P_{partial}$ or C_{room} if indoors].

Mechanisms of Vapor Generation

The liquid and its vapors are **always** considered to be in equilibrium with each other right at the liquid-air interface. The concentration of a vapor in equilibrium is (by definition) its vapor pressure [P_{vapor}]. P_{vapor} can be equated to C in mg/m³ and to ppm. The latter equation is written here as Equation D-1 because of the practical importance of ppm (*cf.*, C which also depends upon the chemical's molecular weight).

$$ppm\ at\ the\ source = \frac{P_{vapor} \times 10^6}{P_{atmosphere}} = \frac{P_{vapor}\ [mmHg] \times 10^6}{760\ [mmHg]} \qquad \text{Eqn. D-1}$$

These conditions set the parameters for what is modeled as molecular diffusion across that boundary layer. Thus, the evaporation rate is largely determined by a set of environmental conditions and one chemical-dependent condition: the chemical's vapor pressure. The chemical engineer's equation to predict evaporation rate is somewhat more complex than needed for field applications (Bird *et al.,* 1960; Sherwood *et al.*, 1975; Fiegley *et al.*, 1981; Bishop *et al.*, 1982) However, industrial hygiene research has used an equation similar to Equation D-2 in many studies (Fiegley *et al.*, 1981; Bishop *et al.*; Powell, 1984; Säämänen *et al.*, 1991; Braun and Caplan, 1992; Nielsen *et al.*, 1995; Nielsen and Olsen. 1995; Hummel *et al.,* 1996).

$$evaporation\ rate\ [G_{moles}] = (Geom.Coef.)\ (A)\ (V^{0.5})\ (P_{vapor} - ambient\ P_{partial}) \qquad \text{Eqn. D-2}$$

where …

G_{moles} = the evaporation rate in terms of moles of vapor generated per unit of time. Both $G_{mass} = MW \times G_{moles}$ and flux $= G_{mass}/A$ could be created from this equation.

Geometric Coefficient (Geom. Coef.) = an empirical "evaporative mass transfer coefficient" that characterizes the effect of the source geometry (its size and shape) on the thickness of the "boundary layer."

Area (A) = the size or surface area of the volatile liquid (ft^2 or m^2).

Velocity (V) = the velocity of the air passing over the evaporating source (*e.g.*, fpm or m/sec).

P_{vapor} = the vapor pressure of the evaporating chemical at its liquid temperature. The units of P_{vapor} are normally mmHg or Pascals which can be converted to mg/m^3 or ppm.

$P_{partial}$ = the partial pressure (or concentration) of the same vapor in the ambient air passing over the source. The chemical's ambient partial pressure is usually far enough below its vapor pressure, that ambient $P_{partial}$ can be disregarded and omitted, as shown in Equation D-3 and beyond.

$$evaporation\ rate\ [G_{mass}] = (MW)\ (Geom.Coef.)\ (A)\ (V^{0.5})\ (P_{vapor}) \qquad \text{Eqn. D-3}$$

One example of such an evaporation equation was developed for EPA by Caplan for organic solvents evaporating from a smooth surface like a spill of 0.5 to 3 feet in diameter (Caplan, 1989). These authors showed through experimental data that an equation equivalent to Equation

D-4 can predict the evaporation rate of a fairly wide range of organic chemicals from such a smooth surface to within a factor of about 2-fold.

$$G\ [mg/min] = (0.0706)\ (MW)\ (A)\ (V^{0.625})\ (P_{vapor}) \qquad \text{Eqn. D-4}$$

where …

G	=	the vapor generation rate, mg/min.
MW	=	the Molecular Weight, g/mole (added to convert moles to grams).
0.0706	=	the empirical "geom.coef."
A	=	the surface area of the liquid source, ft².
V	=	the air velocity over the liquid surface, ft/min.
P_{vapor}	=	the vapor pressure of the evaporating substance, mmHg.

In contrast to comments made within the Agency's background document, the value of a chemical's molecular diffusion coefficient has a minor impact on volatilization (due to the relatively narrow range of values of that coefficient among the chemicals of interest, such as a range of 1.11x among those pesticides in the white paper's Table 3) and even less of an impact on plume dispersion (in contrast to eddy diffusion in dispersion). Eddy diffusion is the dominant mechanism below and to the right of the line in Figure D-2 representing the 1.5×10^{-5} m^2/sec molecular viscosity of air (Smagorinsky, 1974; Smagorinsky, 1981; Atkinson, 1995). Molecular diffusion is too slow to be an important chemical transport mechanism *except* either over very small distances or over very long times.

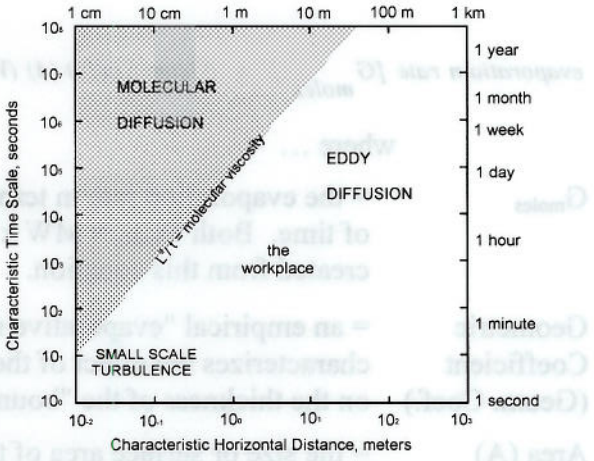

Figure D- 2. Adapted from Smagorinsky (1981).

Dilution of Vapors from Continuous Evaporation

The steady state concentration [C in mg/m³] equals the mass rate of evaporation (or G_{moles} HMW) divided into some apparent volumetric flow rate of fresh air (Q in m³/min) into which the contaminant appears that it is being diluted, as depicted by Equation D-5.

$$steady\ state\ C\ [mg/m^3] = \frac{G_{mass}\ [mg/m^3]}{Q_{apparent}\ [m^3/\min]} = \frac{G\ [moles/mim] \times MW}{Q_{apparent}\ [m^3/\min]} \qquad \text{Eqn. D-5}$$

It is important to understand that the subscript "apparent" is used because the plume of contaminant represented by "G" is not diluted into any easily definable volume flowing per minute (except in the case of thorough mixing inside a room served by general ventilation). It only appears to be diluted because the concentration [C] at any location is always less than C equivalent to P_{vapor} at the source. The amount of dilution will depend, for example, upon one's orientation and distance from the source.

At least in theory, Equations D-3 and D-5 could be combined into Equation D-6 (or Equation D-7) to predict the average concentration from continuous evaporation to which someone would be exposed. The concept is theoretical not only because "Geom.Coef." is difficult to predict for most sources (*e.g.*, a task relegated to PRZM or PEARL for pesticides) but also because $Q_{apparent}$ would depend upon the air flow pattern and the person's proximity to the source and the plume in a way that is currently difficult to predict (a task relegated to PERFUM). Nonetheless, this equation can be manipulated to good effect as explained below.

$$vapor\ C\ [mg/m^3] = \frac{(Geom.Coef.) \times (Area) \times V^{0.5}}{Q_{apparent}} \times MW \times P_{vapor} \qquad \text{Eqn. D-6}$$

$$vapor\ ppm = \frac{(Geom.Coef.) \times (Area) \times V^{0.5} \times 24.45}{Q_{apparent}} \times P_{vapor} \qquad \text{Eqn. D-7}$$

The arrangement of the variables within Equation D-7 suggests that the ppm vapor concentration at any location in the vicinity of an evaporating source can be viewed as having two groups of determinants: a group of environmental determinants (those that comprise the "ratio" on the right side of Equation D-7) and a chemical determinant (the chemical's vapor pressure on the far right side of Equation D-7).

- None of the **environmental determinants** of exposure within either Equation D-6 or D-7 have anything to do with the chemical *per se*. The numerator in the parentheses comprises only the physical characteristics of the source that affect its evaporation or flux rate. The denominator encompasses only the physical mechanisms that dilute the plume in the pathway from the source to the specific location at which the vapor concentration is being described. Together, this whole group of environmental variables determines by how much the vapors will get diluted between the P_{vapor} concentration existing at the source and the concentration [C] at the location of interest in an exposure scenario. Environmental factors only affect dilution, and (other than how temperature affects vapor pressure) they do not affect the initial vapor concentration at the source.

- The singular **chemical determinant** of exposure on the far right side of Equation D-7 has nothing to do with the environment in which the chemical is being used (again other than the source temperature affecting vapor pressure [P_{vapor}]. Popendorf (2006) showed that a temperature increase of approximately 12°C or 21°F is required to double the P_{vapor} of a wide range of organic solvents. This is less of an effect than many other factors affecting

vapor exposures to a pesticide such as its vapor pressure at normal temperature (spanning 4 to 6 orders of magnitude). Thus, the chemical component only affects the source of exposure, not the pathway or its dilution.

Most aerosols (except for fumes) have virtually no chemical-specific vapor pressure, but an equivalent G [mg/min] for aerosols can be defined for any particular aerosol source. Once an aerosol is generated, its dilution generally still depends only on $Q_{apparent}$ (as long as sedimentation is not important) (Bémer *et al.*, 2000). Thus, an aerosol concentration could be predicted using Equation D-6 in much the same way as for vapors if the aerosol generation rate G and environmental dilution due to $Q_{apparent}$ were known. However, $Q_{apparent}$ can rarely be predicted quantitatively in practice.

This partitioning allows one to examine the environmental determinants of exposure separate from the chemical determinants. Equation D-8 isolates the environmental determinants by dividing Equation D-7 by P_{vapor} and inverting. The resulting ratio is the amount by which the vapor pressure concentration at the source [P_{vapor}] is diluted to create the resulting concentration at any location. Because the ratio in Equation D-8 is the amount of dilution created by the environment, this ratio is called the "Environmental Dilution Ratio" or EDR. Again notice that all of the variables that comprise the EDR relate to the environment, not to the chemical being used in that environment. This ratio is unitless as long as the units of concentration in both the numerator and denominator are the same.

$$EDR = \frac{P_{vapor}\ converted\ to\ C\ or\ ppm}{C\ or\ ppm\ at\ a\ defined\ location} = \frac{Q_{apparent}}{(Geom.Coef.) \times (Area) \times V^{0.5}} \qquad \text{Eqn. D-8}$$

Separating the environmental from the chemical determinants of exposure allows chemical hazards to be viewed in a new way. In the traditional view, a chemical's concentration is either measured or predicted, then its acceptability is based on the ratio of the chemical's exposure limit [denoted herein as EL in units of either mg/m³ or ppm] to that chemical's measured or predicted concentration [denoted herein as either C or ppm and must be in the same units as the EL]. In the occupational health field, *e.g.*, within OSHA, this ratio must be greater than one to be acceptable, as expressed by Equation D-9a. To relate the occupational health field approach to EPA's MOE approach, the ratio of EL/C would need to exceed the pesticide's MOE, as defined in Equation D-9b.

Whether an acceptable ratio is 1 (as in Eqn. D-9a) or an MOE (as in Eqn. D-9b) is a policy decision outside the purview of this summary.

$$\frac{Exposure\ Limit\ [EL]}{measured\ or\ predicted\ C\ or\ ppm}\ must\ be > 1 \qquad \text{Eqn. D-9a}$$

$$\frac{Exposure\ \ Limit\ [EL]}{measured\ \ or\ \ predicted\ \ C\ \ or\ \ ppm}\ must\ \ be > MOE$$ Eqn. D-9b

Knowing that P_{vapor} (or its equivalent in either ppm or mg/m³) is the maximum concentration at which a given chemical can exist as a vapor, one can anticipate that the maximum hazard that a chemical's vapor can **potentially** create is equivalent to the ratio of how much greater P_{vapor} is than its exposure limit. The "Vapor Hazard Ratio" or "VHR" as expressed mathematically in Equation D-10 is the maximum potential hazard that a given chemical's vapors can generate.

$$VHR = \frac{P_{vapor}\ \ in\ units\ \ of\ \ ppm\ \ or\ \ mg\ /\ m^3}{Exposure\ \ Limit\ [EL]\ in\ the\ same\ units}$$ Eqn. D-10

The two properties that comprise the VHR (its vapor pressure and its exposure limit) are both intrinsic to a given chemical (and have nothing to do with the environment *per se*). Together, they specify the minimum amount by which a given chemical's vapor needs to be diluted by the environment to reduce its concentration from its vapor pressure at the source to its exposure limit in the breathing zone. If the vapors in some one's breathing zone are not diluted by as much as the chemical's VHR, then that person will be overexposed. In terms of EPA's MOE approach, the vapors must be diluted by the VHR times a desired MOE, *e.g.*, VHR x 100.

Nothing is wrong with evaluating acceptability as simply the ratio of measured results to an exposure limit, but the separate concepts of chemical dilution and environmental dilution can be re-combined advantageously. Think of looking at evaluation as a process of comparing the amount of dilution that a given chemical needs to the amount of dilution that a given environment actually creates. In terms of the MOE approach, this alternative view of evaluation is the same as asking if the Environmental Dilution Ratio in someone's breathing zone is sufficiently greater than the Vapor Hazard Ratio for the chemical being used, as expressed in Equation D-11.

$$\frac{C_{measured\ or\ predicted}\ /\ P_{vapor}}{EL\ /\ P_{vapor}} = \frac{EDR}{VHR}\ must\ \ be > MOE$$ Eqn. D-11

Conceptually viewing acceptability in its separate chemical and environmental components can yield several benefits. For instance, one could anticipate that a given chemical should only be used in an environment that can dilute the vapors reaching a given population (the "EDR" for that setting) by as much as the toxicity of a given chemical requires its vapors to be diluted (the chemical's "VHR" times the applicable MOE). If an evaluation reveals that a defined population is being overexposed, then one can conclude that the environment cannot create sufficient dilution for the chemical being used. One could then compare the advantages of attempting to achieve an acceptable solution either by reducing the chemical's intrinsic VHR (*e.g.*, by substituting an intrinsically safer chemical) or by increasing the environment's ability to dilute a

chemical reaching someone's breathing zone (*e.g.*, by modifying or restricting the use conditions).

This concept could also be used in setting priorities for both pesticides with intrinsic vapor hazards and use-settings susceptible to creating vapor hazards. Table D-1 within this appendix lists the VHR for about 40 pesticides based on their industrial exposure limits (TLVs are intended for manufacturing settings, see Braun and Caplan, 1992). The VHRs in this table span over 11 orders of magnitude and 9 orders of magnitude excluding fumigants. For those chemicals with a VHR less than 1, its saturated vapors are less than its exposure limit, meaning they can only over-expose someone as an aerosol. A similar list could be generated to rank-order the pesticides of interest to the Agency, but using HEC or RfC concentrations in the denominator (instead of C). Such a list, the Panel noted, could interface with an array of Environmental Dilution Ratios (EDR values based on flux rate and dispersion scenarios modeled by PRZM, PERFUM, *etc.*) to potentially refine the Agency's priorities in terms of use-settings.

Table D-1. Pesticides that had an ACGIH TLV® in 2005 are listed in rank-order of their Vapor Hazard Ratio (VHR = P_{vapor} x 10^6 / TLV x 760). The compound's vapor pressure [P_{vapor}] is at 25°C unless otherwise indicated. Where the mass concentration is given in parentheses, the TLV® in ppm = C x 24.45/MW. Adapted from Popendorf (2006).

Chemical Name	TLV® [mg/m³]	CAS#	TLV [ppm]	P_{vapor} [mmHg]	VHR
Carbon disulfide		75-15-0	10	358.	47,105
1,3-Dichloropropene		542-75-6	1	34.	44,737
Epichlorohydrin		106-89-8	0.5	16.4	43,158
Dichlorvos (DDVP)	0.1	62-73-7	0.011	0.053	6,303
Diazinon	0.01	333-41-5	0.0008	0.0112	1,834
Ethylene dibromide (EDB)		106-93-4	20	11.	724
Naled	0.1 at 20°C	300-76-5	0.0064	0.002	410
Mevinphos (Phosdrin)	0.01	7786-34-7	0.0011	0.00013	157
Heptachlor	0.05	76-44-8	0.0033	0.0004	161
Fonofos (Difonate)	0.1	944-22-9	0.0099	0.0002	27
Sulfotep (TEDP)	0.1	3689-24-5	0.015	0.00017	15
Lindane	0.5	58-89-9	0.042	0.00041	13
Aldrin	0.25	309-00-2	0.0168	0.00012	9
Dichrotophos	0.05 at 20°C)	141-66-2	0.0052	8.6e-05	4.4
Chlorpyrifos	0.1	2921-88-2	0.007	1.7e-05	3
Parathion	0.05	56-38-2	0.0042	9.7e-06	3
Fenthion	0.2 at 20°C	55-38-9	0.018	3.0e-05	2.3
Endosulfan	0.1	115-29-7	0.0060	1.0e-05	2
Methyl parathion	0.2	298-00-0	0.0186	1.7e-05	1.2
Carbofuran	0.1 at 20°C	1563-66-2	0.011	5.0e-06	1
Endrin	0.1	72-20-8	0.0064	3.0e-06	6.2e-01
Dieldrin	0.25	60-57-1	0.0160	5.9e-06	4.8e-01
Chlordane	0.5	57-74-9	0.0298	9.8e-06	4.3e-01
Thiram	1	137-26-8	0.102	1.7e-05	2.2e-01
EPN	0.1	2104-64-5	0.0076	9.5e-07	1.7e-01
Fenamiphos	0.1	22224-92-6	0.008	1.0e-06	0.16
Malathion	1	121-75-5	0.074	7.9e-06	1.4e-01
Ronnel	10	299-84-3	0.76	7.5e-05	1.3e-01
Ethion	0.05	563-12-2	0.0032	1.1e-06	0.06
2,4,5-Trichlorophenoxyacetic acid	10	93-76-5	0.96	3.8e-05	5.2e-02
Warfarin	0.1	81-81-2	0.0079	1.2e-07	1.9e-02
Paraquat	0.1	4685-14-7	0.0095	1.0e-07	0.01
Methoxychlor	10	72-43-5	0.7074	2.6e-06	4.8e-03
Carbaryl (Sevin)	5	63-25-2	0.608	1.4e-06	2.9e-03
Diquat (respirable)	0.1	2764-72-9	0.0071	1.0e-08	1.9e-03
Atrazine	5 at 20°C	1912-24-9	0.566	3.0e-07	1.0e-03
Azinphos methyl	0.2	86-50-0	0.0154	7.5e-09	6.4e-04
Temephos	1	3383-96-8	0.52	7.9e-08	2.0e-04
Rotenone	5	83-79-4	0.31	2.6e-09	1.1e-05
Benomyl	10	17804-35-2	0.842	3.7e-09	5.8e-06
Picloram	10	1918-02-1	1.01	7.2e-11	9.4e-08

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